S. HRG. 104–559

# REFORMING HEALTH CARE



## HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED FOURTH CONGRESS

SECOND SESSION

**SPECIAL HEARING**

Printed for the use of the Committee on Appropriations



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# REFORMING HEALTH CARE

THURSDAY, APRIL 11, 1996

U.S. SENATE,
SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES,
COMMITTEE ON APPROPRIATIONS,
*Portland, OR.*

The subcommittee met at 2 p.m., in the Old Library Auditorium, Oregon Health Sciences University, Hon. Mark O. Hatfield presiding.

Present: Senator Hatfield.

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### NATIONAL INSTITUTES OF HEALTH

**STATEMENT OF DR. HAROLD VARMUS, DIRECTOR**

OPENING REMARKS OF SENATOR MARK HATFIELD

Senator HATFIELD. The hearing will please come to order. When the Congress returns after the Passover and Easter recess period, we will be taking up a bill to consider health care reform legislation. This legislation was proposed by my colleagues, Senators Kassebaum and Kennedy, and has strong bipartisan support and is a major step toward fixing problems with our health care system, particularly with regard to the availability and cost of insurance.

However, a vital element of health care reform is not part of the Kassebaum-Kennedy bill. This element is the focus of today's hearing, how much and how best to maximize the return on our Federal investment in medical research. I am sure that most of you know that we do have over $12 billion invested annually. That not only includes NIH, but that includes Defense, Veterans, et cetera, so we are investing a very tidy amount of money annually to support biomedical research, which to me is a central element of health care reform. What better way to lower health care costs, to reduce suffering and increase productivity than to prevent and cure disease?

The proud tradition of American leadership in the biomedical sciences, conceived over 100 years ago and embodied today in the activities of the National Institutes of Health, has been important and one of the great factors in our domestic quality of life as well in our international stature. Two key objectives drive the engine of biomedical research and the first is to expand fundamental knowledge about how living systems exist and function, commonly known as basic research. The second is to apply that fundamental knowledge to the prevention, treatment, and cure of disease, commonly

known as clinical or patient-oriented research. And there may be other definitions, I am very quick to add.

Both aspects of research are essential because they depend upon each other, and without the foundation of basic research, progress in clinical research would be impossible. Conversely, without the expertise of the clinical researcher, the basic scientist would have no means of translating discoveries into treatments for real people. There is no question that the objective of expanding our basic science knowledge has been a resounding success.

There has been an explosion of information in the basic sciences and we stand at the threshold of great and further new discoveries. Through the Federal investment over the last century, scientists have begun to unlock the mysteries of genetics and molecular medicine, which have the potential to provide powerful new weapons in fighting disease.

But will these discoveries be taken to the next step and converted into tools to prevent, treat, and cure disease? Will we apply this knowledge to the treatment and prevention of disease? Is the medical research enterprise in this country equipped and ready to harness this powerful information and develop the new weapons necessary to win the war against disease; such as cancer, heart disease, and AIDS, now noted as the big three in the medical research field in size of their grants?

Despite the clear societal and economic benefits, the answer appears to be a resounding, "no." Separate reviews by the NIH internal panel and the Institute of Medicine [IOM] in 1994 sounded the alarm that clinical research today is in crisis. The IOM report concluded with this language: "The committee believes that the human resource pool will be seriously deficient for conducting investigations with human subjects in the near future, if it is not already." The November 1994 NIH clinical research study group commissioned to determine if patient-research oriented grant applications received fair review, amplified the problems facing clinical research today.

In their view, the group found that there was a significant degree of frustration and anger in the patient-oriented research scientific community about NIH's review of applications and that patient-oriented research applications do fare less well than laboratory-oriented research applications.

On January 26 of this year, I introduced legislation to take steps to resolve the crises in clinical research and to get us back on track to achieve both our objectives of expanding fundamental knowledge and applying that knowledge to people. S. 1534, entitled the Clinical Research Enhancement Act of 1996, would implement many of the recommendations of the IOM panel and create a stabilized funding base for clinical research as well as new incentives for expanding the pool of clinical researchers in this country. My legislation is supported by over 80 national advocacy groups.

I hope that today's hearing will provide a springboard for action for shoring up our foundation for clinical research, for it is only through meeting both key objectives of research that our Nation can maximize its return on the investments of dollars both in terms of reducing health care costs and relieving human suffering.

I want to thank all the other witnesses today for your participation in this hearing and I look forward to your testimony. I also want to thank Dr. Kohler and Oregon Health Sciences University for hosting this hearing. Now we will proceed to the first panel.

Our first witness is Dr. Harold Varmus. For the past 2½ years, Dr. Varmus has served with great distinction as the Director of the National Institutes of Health. He is a Nobel laureate who brings great strength and insight to the job as NIH director. I can say from personal knowledge that his relationships to the Hill and to other parts of the political community in Washington have been carried on with the highest degree of professionalism, understanding, insight, and intelligence.

I want to thank you, Dr. Varmus, for setting aside time to participate in this hearing today and as I told you awhile ago, your entire written statement will be included in the record in full and you are free to proceed as you wish in terms of adding to this hearing. Thank you for being here.

SUMMARY STATEMENT OF DR. HAROLD VARMUS

Dr. VARMUS. Thank you, Mr. Chairman. It is a great pleasure for me to be here. As I am sure the audience knows very well, you have achieved a status somewhere between a hero and a saint in the biomedical community. It is with great respect for you that I come here today to provide this testimony.

I suspect the NIH needs very little introduction to this audience, but I feel I must say a couple of things about the Institution. As Senator Hatfield's comments make clear, the NIH bears the major responsibility for Federal support of biomedical research, with a budget of nearly $12 billion this year, 24 Institutes and Centers that are devoted to research on a wide variety of diseases—both the common diseases the Senator alluded to, such as AIDS, heart disease and cancer, but also many rare diseases that we may speak of later—using a wide diversity of research tools to pursue research on these maladies.

We do research in an intramural program, largely in Bethesda, that commands about 10 percent of our budget, but most of our money goes to extramural investigators in the research community around the country, 1,700 different institutions in all States and territories. In Oregon, for example, we award grants that total a little over $100 million, at about 26 institutions, with nearly one-half of that money being received by investigators here at the Oregon Health Sciences University.

The components that are required for success in biomedical research are at least four. The two major ones the Senator has already alluded to—basic or laboratory dependent science and clinical, sometimes known as patient-oriented research. Two others are the transfer of technology into industry and the communication of our findings to the public. All of these endeavors must be working well in a complex set of interactions for success to occur. In my written testimony, I have supplied many examples of ways in which these four components of our enterprise have worked effectively in the past.

Let me illustrate the principle with just one case, the case of the protease inhibitors, new pharmaceutical agents that have recently

been approved by the FDA and appear to be the most effective agents to date for the treatment of HIV. Those new pharmaceuticals were made possible because as long ago as the early 1970's, investigators working with retroviruses—in an age before AIDS was even known as a disease and before human retroviruses were known—and elucidated the ways in which retroviral proteins were made and the need for an enzyme to chop those proteins into pieces.

That basic research then became a focus of attention after AIDS was understood, and it was apparent that interference with the growth of HIV would be fundamental to treatment of the disease. Once the protease, an enzyme that cuts up viral proteins, was isolated by basic scientists and analyzed in three-dimensional form, then the problem was moved into the industrial sector with pharmaceutical houses screening for effective drugs and then manufacturing them, then coming back into the academic sector for clinical testing of agents. So again, a complex interaction among several segments of our community was required for this major advance.

## CLINICAL RESEARCH

In general it's my view that the NIH and its multiple approaches to disease are working quite well. But in all components that I have mentioned there are difficulties. Perhaps nowhere among the four components that I mentioned are those difficulties more apparent than in the area of clinical research, the main object of our discussion today. In the area of clinical, patient-oriented investigation, there are many chronic problems, in particular the difficulty of recruiting investigators, a problem that has been recently dissected by the Institute of Medicine.

We know that the burden of debt and the difficulties of doing and funding clinical research are disincentives for people to enter the field. We are also particularly concerned about recruiting more minority investigators into clinical activities for reasons we could discuss later.

For many years there has been a paucity of appropriate training programs, particularly training programs that teach the difficult specific task of doing clinical research and link individuals who have a firm grounding in basic science with clinical problems. We have a chronic problem with facilities for doing clinical research—not so much here on this campus where you have managed to build some extraordinary buildings—but in many places around the country, including the NIH intramural program, where our clinical research facilities are over 40 years old and in need of replacement.

There are new problems in clinical research as well. The challenge of managed care has had a major effect on academic health centers around the country where most of our clinical research is done with loss of dollars from patient care revenues and loss of patients into clinical trials. Clinical investigators have, at least in some categories, been affected by relatively low success rates when they apply for grants as documented by the report from Gordon Williams, about which you will hear more later.

Clinical research is also challenged by new paradigms for doing medicine. The advances that the Senator alluded to in genetics and molecular biology and immunology are going to create tremendous

new opportunities for applying science to clinical problems But in order to do that, we have to have investigators in the clinical arena who are well-trained in those areas and who interact usefully with their colleagues in basic sciences. It has been my observation and concern that there is, in many places, an enlarging gulf between clinical investigators and bench scientists.

I want to congratulate the Senator for paying special attention to the problems of clinical research because too often it does not receive the attention it might deserve, with basic science in the newspaper every day whenever new discoveries are made.

We too at NIH have been paying attention to the problems with clinical research. I would like to describe very briefly some of the initiatives that have been taken since I arrived there 2½ years ago to help to counter some of the difficulties that I have mentioned. Many of the initiatives that I will be alluding to briefly are described in more detail in my written testimony, and perhaps we can pursue some of them in the question-and-answer period.

First, about a little over 1 year ago, we put together a clinical research panel headed by David Nathan, currently the president of the Dana Farber Cancer Center. This panel has been asked to serve for at least 3 years to address a number of very broad issues having to do with the financial support of clinical research, the conditions of facilities for doing clinical research, and the nature of training programs in clinical investigation. There are other goals as well. The intention here is an action plan. We know there are problems. This panel is intended to develop action items upon which I and Institute Directors can move forward.

Second, we are paying attention to the revitalization of the clinical research center at the NIH. The clinical center at NIH is the place where roughly 50 percent of all clinical research beds are located, and it has a variety of problems. We have taken at least four methods to improve the situation.

First, we are changing many of the operations of the clinical center in response to a Department of Health and Human Services report that was recently published after a fact-finding examination of our operations by Helen Smits, the Deputy Administrator of HCFA.

Second, we are proposing the construction of a new clinical research hospital that will be funded, we hope, through an appropriation request that appears in the President's budget for 1997.

Third, we have developed some imaginative training programs, including a course in clinical research which has attracted hundreds of students and is being further developed in collaboration with Duke and Johns Hopkins Universities and is being used more broadly around the country. We also have developed a loan repayment program that is currently enjoyed by 19 clinical trainees at the NIH.

Finally, we have experimented with new kinds of outreach to the extramural communities so extramural clinical investigators can make use of our resources at the clinical center.

In the third broad area of activity, we have done some new experiments in recruitment of patients into clinical research activities. The most prominent of these was announced 3 weeks ago when the National Cancer Institute, represented by Richard Klausner, the new director, and the Department of Defense, rep-

resented by Steve Josephs, announced an agreement by which patients who are in the military or in military families can participate in NCI-sponsored clinical trials with reimbursement of their clinical costs by the CHAMPUS insurance program that supports DOD families.

We see this as a potential model for similar reimbursements in many other disease categories, and we see it as a model for approaching many other insurers, inside or outside of government, who might support the costs of care that go hand in hand with much clinical research.

Fourth, we are paying additional attention to our extramural training programs for clinical investigators. The numbers of positions are currently rising. The number of K awards that support clinical investigators has gone from roughly 500 to nearly 800 in the current year. The number of clinical associates in the CAP programs managed within general clinical research centers [GCRC's] has gone from about 50 to 100 over the last couple of years. We are also interested in pursuing legislative authorities for a loan repayment program to further induce outstanding medical students who have incurred deep debts to enter clinical research.

We are trying to respond in a variety of ways to the critique of the peer review system made by the Williams report. We have developed a peer review oversight group that will have among its charges the goal of putting into action those recommendations in the Williams report that we subscribe to. I am currently in the process of hiring a new director of the division of research grants who will be paying special attention to the way in which clinical research is reviewed.

Finally, I have taken a personal interest in novel means to foster a richer interaction between basic scientists and patient-oriented investigators and we can discuss some of those a little later if you would like.

PREPARED STATEMENT

Finally, Senator, I would like to say it has been a privilege for me to come out here and to describe some of the things that NIH is doing and to try to address some of the concerns that we share about the status of clinical research. I would be pleased to answer any questions you might have about my testimony, either written or spoken.

[The statement follows:]

PREPARED STATEMENT OF HAROLD VARMUS, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Mr. Chairman: I am pleased to participate in this important hearing and to tell you about our efforts to improve the Nation's health through medical research sponsored by the National Institutes of Health (NIH).

ORGANIZATION AND ROLE OF THE NIH

In 1940, President Franklin Roosevelt dedicated the grounds of the NIH and first few buildings of the new Bethesda campus. As the Nation braced itself against a world descending into war, the President reminded America that our "total defense involves a great deal more than building airplanes and ships, bombs and guns. * * * We cannot be a strong nation," he said, "unless we are a healthy nation."

After 5½ decades of growth, the NIH of today is the largest and most successful medical research institution in the world, with a budget of nearly $12 billion and

a major impact not only on this Nation's health, but on health status worldwide. More than eight out of every ten research dollars appropriated to the NIH flow out to the scientific community across the Nation, primarily in the form of peer-reviewed research grants. Today that community numbers more than 50,000 investigators affiliated with nearly 2,000 universities, hospitals, and other research facilities located in all 50 states, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad. Approximately 10 percent of the NIH budget supports a program of basic and clinical research activities administered and staffed by our own physicians and scientists. In addition to basic research laboratories, this in-house, or intramural, research program includes a research hospital, the NIH Clinical Center. Each year, more than 20,000 children and adults from all over the country, and some from abroad, are referred to the Clinical Center for experimental treatment and study.

Today's NIH is a federation of 24 Institutes, Centers and Divisions that seek to expand knowledge about living systems and apply that knowledge to improve human health. Perhaps the best known NIH research institutes are those that focus either on a particular disease, such as the National Cancer Institute, or on an organ system, such as the National Heart, Lung, and Blood Institute. Other Institutes and Centers attend to overarching scientific needs and opportunities, such as the National Center for Human Genome Research, while others focus on stages of human development, such as the National Institute on Aging. Other NIH components are responsible for developing the array of technologies and resources that are vital to innovative and efficient research; for example, the National Center for Research Resources oversees the General Clinical Research Centers, which provide core resources, such as specialized personnel and sophisticated laboratories, to clinical investigators around the country.

Multiple Institutes and Centers often address different aspects of a single health problem faced by our citizens. For example, research on Alzheimer's disease takes place in Institutes devoted to neurology, aging and mental health. This feature, which is essential to the research effort, requires close interactions among the Institutes and Centers; these may be informal (such as scientists talking with one another), or they may be guided by inter-Institute committees or by NIH-wide coordinating offices that are located in the Office of the Director (e.g., the Office for Research on Women's Health.) This rich matrix of research activity requires open and collegial dialogue among the Institutes and Centers and thrives in an atmosphere that maximizes flexibility in the pursuit of knowledge. A major objective of my administration at the NIH has been the enrichment of these interactions and a strengthening of the sense of unified purpose.

## HOW NIH WORKS TOWARD THE GOAL OF IMPROVED HEALTH

The human body is complex and the diseases to which it is susceptible are legion. So we approach the goal of improving the Nation's health aware that many experimental strategies require years, often decades, of effort to make major advances against each disease.

While no single pathway can be described as the common route to success, it is apparent that many advances demand the talents of laboratory scientists who work on fundamental aspects of living organisms; clinicians and epidemiologists who describe the conditions we attempt to prevent or cure; clinical investigators who use their knowledge of both disease and scientific advances to devise and test new therapeutic or preventive strategies; and industry-based scientists who finally develop new drugs and devices and help to bring them to market. This means that NIH must provide financial support for many kinds of work and promote training programs that develop talented people to do the work.

It is important to understand that most NIH-funded research is "investigator-initiated." That is, the research ideas we fund are proposed by the scientists themselves, not by the NIH. By sustaining our traditional standards of scientific excellence through peer review, the NIH uses competition among the most highly trained scientists in the world to ensure that Federal funds are distributed to the most promising research projects; at present, only one out of four meritorious proposals can be funded. However, because of the broad constellation of public health needs, scientific opportunities, Executive and Congressional interests, and other factors that bear on the course of the Nation's investment in medical research, the NIH must constantly reevaluate its programs and have the flexibility to make necessary changes.

The process of examining research priorities is not reducible to a simple flow chart or time line. It takes place at several distinct levels in the NIH organization and is occurring all of the time. Priorities are set both within the Institutes and

Centers by their Directors; but, as Director of the NIH, I assume ultimate responsibility for the overall distribution of funds among our research programs.

The NIH must also ensure that the cadre of scientists we fund have adequate facilities and equipment to conduct their work. In fact, many of the advances in medical research that are leading to ever more effective treatments for illness reflect stunning innovations in sophisticated, but often costly, research technologies that are far beyond the capacity of all but a handful of institutions to purchase, construct, or maintain. NIH recognizes that ensuring broad access to these research resources creates efficiencies that make the research dollar go farther, while providing critical resources to all scientists. Often, access to the needed tools by the largest possible number of scientists determines the pace of research on many devastating illnesses.

A partial solution to the problem of expensive technologies and scarce resources already exists, and is being practiced through innovative "shared resource" centers funded by NIH. For example, NIH's National Center for Research Resources funds one shared resource network, built around its Shared Instrumentation Grant Program, that involves some 60 biotechnology centers around the country. At present, more than 7,000 investigators use the network for about 5,000 research projects. Another example is the Frederick Biomedical Supercomputer Center in Frederick, Maryland, a resource for the world's medical research community. Through this center, scientists working out of their home institutions can obtain assistance in the use of the latest computational methods to exploit and refine biological research techniques and amass data important to their research.

Emphasis on sharing research resources is a relatively new phenomenon brought about by increased sophistication and cost, but progress in medical research and the practice of medicine has always required sharing of information. The NIH has a longstanding tradition of providing a steady flow of information about important research discoveries and other medical information to the research community, to health care providers, and to the general public.

For example, one of the primary mandates of NIH's National Library of Medicine is to ensure that health professionals around the world have access to the latest published medical knowledge. Last year, users of MEDLINE, a database with eight million references and abstracts to medical journal articles, conducted 7.5 million searches. Half of these searches were for purposes of patient care and were conducted in hospitals, clinics and the offices of individual health care providers. This vital information base connects health care professionals in even the most rural areas of the country to the latest medical advances.

Another way in which the NIH communicates the results of medical research is through "clinical alerts." These provide health-care practitioners with immediate news of significant research results that affect clinical care. The full range of electronic and print media are employed in these instances to ensure immediate attention to the lifesaving (or life-threatening) potential of the latest research findings.

NIH is also an invaluable resource for the general public, including the nearly two million people who directly request medical and health information each year. NIH's Cancer Information Service alone (1–800–4–CANCER) handles more than 600,000 telephone inquiries annually. The recently created NIH Home Page on the World Wide Web will soon include 110 of the "best selling" consumer health booklets from the NIH. In an effort to explore new ways of reaching the public, NIH recently funded two pilot episodes for Health Week, a Maryland Public Television news magazine about health, covering such topics as spinal cord injury, angiogenesis in cancer and heart disease, melatonin, and the obesity gene. A unique aspect of the program is the provision of "access points"—phone numbers, Internet addresses and mailing addresses—to give the public avenues exploring the health issues covered in greater depth.

To fully reap health benefits from the knowledge gained through fundamental investigations, NIH must have in place efficient processes for transferring knowledge and technology from NIH-funded programs to the private sector, where biotechnology and pharmaceutical firms are poised to translate what we produce into products that improve health and prevent disease.

NIH's technology transfer effort in its intramural research program relies on two principal mechanisms, Cooperative Research and Development Agreements (CRADAs) and the patenting and licensing of research inventions. Over the decade ending with fiscal year 1995, NIH intramural scientists negotiated 269 CRADAs with private organizations to support a wide range of research activities. Between 1985 and 1995, NIH was awarded 560 patents on inventions made by our intramural scientists, and we negotiated 713 licenses to develop commercial applications based on those patents. The products that resulted from these patents include a simple, accurate and inexpensive screening test for HIV infection that also can be

used to monitor and ensure the safety of public blood supplies; two major therapeutics against HIV-infection; and vaccines for the treatment of Hepatitis A and for treatment of chronic B-cell leukemia.

Recipients of NIH support in the extramural community promote technology transfer by two analogous mechanisms. Each institution is entitled under the Bayh-Dole Act to seek patent protection and licensing arrangements for the inventions made by their employees while working with NIH funds. In addition, many of these institutions have negotiated agreements that allow NIH grantees to receive additional support from industries for separate research projects. Another extremely important means of technology transfer involves the traffic of personnel, especially from NIH-supported graduate and post-doctoral training programs to jobs in the industrial sector. The vitality of NIH research programs, therefore, has a direct impact on the strength of our Nation's industry, since the workforce in the pharmaceutical and biotechnology fields is trained to do science in the context of our training and research activities.

ADVANCES IN MEDICAL RESEARCH THAT HAVE LED TO CHANGES IN CLINICAL PRACTICE

To have an impact on improving health and combating disease, scientists need to develop and work from a body of basic knowledge. The path leading from new findings to changes in clinical practice can be very long, often measured in decades. Many of the dramatic changes that have occurred in American medicine over the past fifty years are based on insights drawn from the traditional biomedical sciences, such as microbiology, physiology, pathology, immunology, and chemistry. The following brief stories about important, relatively recent developments in the prevention and treatment of disease illustrate some of the ways in which new knowledge has gradually led to improvements in the country's health.

—Haemophilus influenzae type b (Hib) is a serious bacterial infection that once affected almost 25,000 children in the U.S. every year, especially infants. Of the nearly 15,000 infants affected by Hib-related bacterial meningitis, up to 10 percent died and 20–30 percent of the survivors suffered permanent health consequences, especially mental retardation. In 1985, based on an understanding of the unique chemical nature of Hib antigens and the epidemiology of Hib in children compared with adults, scientists developed the first effective vaccine against Hib for children older than two years. But to make a vaccine effective for infants, it was necessary to exploit decades of research in chemistry and immunology to develop a novel technology that linked sugars from the outer coat of the Hib bacterium to an immunity-boosting protein. Today, thanks to the new vaccines, Hib disease has decreased by over 95 percent among infants as well as children; the vaccines have been estimated to save more than $400 million per year.

—Cancer of the testis is a relatively rare cancer afflicting about 5,000 men annually, but it usually strikes young men, 20–40 years of age. In 1965, a biophysicist working at Michigan State University made an unexpected observation that ultimately changed the outlook for men with testicular cancer: he found that when an electric current was generated with platinum electrodes in a bacterial culture, normal cell division was inhibited. The inhibition of cell division was soon found to be caused not by the electric current, but by the generation of a small amount of a well-known chemical, cisplatin, from the platinum electrodes. After much collaborative work with the National Cancer Institute and a pharmaceutical firm, scientists found that cisplatin could inhibit cell division in other cells, especially cancer cells. Later, it was recognized that testicular cancers responded especially dramatically to cisplatin. Today, after two decades of medical research based on an observation in biophysics, testicular cancer has been transformed from a nearly uniformly fatal disease to one that is 80–95 percent curable. Cisplatin is not only responsible for saving lives; a cost-benefit analysis of cisplatin-based chemotherapy estimated an annual savings of $150 million, mainly due to savings from the future earning potential of survivors.

—A half million Americans each year suffer from strokes, four out of five of which are caused by a blood clot that blocks blood flow to the brain. Years of NIH-supported laboratory research on the biochemistry of blood clotting was essential to the development of clot-dissolving drugs such as tissue-plasminogen-activator (t-PA), which has been successfully used in treating heart attacks triggered by blood clots. More recently, researchers have shown that t-PA is an effective emergency treatment for stroke caused by blood clots when given within three hours of initial symptoms. Among stroke victims to whom the drug was administered in rigorous clinical trials, the proportion who made excellent re-

coveries after three months increased by 30–50 percent. This is the first effective therapy for stroke, stimulating work toward better therapies with even greater preservation of brain function.

—Research begun as a study of cholesterol in a rare disease ultimately led to an effective treatment for all people suffering from high blood cholesterol, a condition that can inhibit blood flow and lead to heart attack or stroke. This built-up cholesterol is derived from low density lipoprotein, or LDL, in the blood. Basic research more than two decades ago revealed that the level of LDL in the blood is regulated by the LDL receptor. This receptor, which is found on the surface of many cells, binds to circulating LDL and removes it from circulation by taking it into the cell, where it is broken down and used by the cell. In studying patients with familial hypercholesterolemia, a rare inherited form of high blood cholesterol, investigators discovered that LDL receptors were either nonfunctional or severely defective. The discovery of this receptor has revolutionized the understanding of cholesterol and lipoprotein metabolism. Each step in the cellular processing of cholesterol has now been meticulously defined. For example, it is now known that the enzyme HMG CoA reductase is required for cholesterol synthesis. Inhibition of this enzyme by a class of drugs called "statins" forces the body to make use of cholesterol in the blood. Thus, these drugs significantly reduce blood cholesterol levels, decrease heart attacks and strokes, and extend life in patients with mildly to severely elevated cholesterol.

—A long-term investment by the NIH in the molecular composition of viruses, especially retroviruses, is directly responsible for recent successes in the production of drugs effective against HIV, the cause of AIDS. The most potent of these drugs are inhibitors of an essential viral enzyme called a "protease," an enzyme that cuts viral proteins into their working components. Retroviral proteases were first discovered in viruses found in chickens and mice; later, research revealed that retroviruses cannot replicate—or reproduce themselves—without proteases. Because HIV is also a retrovirus, scientists theorized that inhibiting HIV protease might block replication of the virus and could lead to a new treatment for AIDS. The pharmaceutical industry subsequently identified and developed agents that can inhibit HIV protease. These therapeutic agents appear to be the most effective and least toxic drugs now available to combat HIV.

### FUNDAMENTAL RESEARCH FINDINGS PRESAGE ADVANCES IN HUMAN HEALTH

Many of the recent advances in the control of disease, such as those described in the preceding section, emerged from discoveries made in the past several decades, and even a century ago, about microbes, the immune system, hormones, and metabolic pathways. Today, we are in the midst of a scientific revolution based on gene isolation, DNA sequencing, sophisticated molecular and cell biology, neuroscience, and study of the three-dimensional structure of proteins. Based on our collective experience with clinical advances developed from earlier discoveries, it is reasonable to anticipate that new and more effective means to combat a host of diseases will emerge over the next few decades from the current transformation of biological sciences. Although it is impossible to predict exactly what those means will be, there are many signs of new trends in clinical practice.

—Efforts to map human genes and determine the sequence of the human genome are progressing at a greater than anticipated pace. Over the past few years, investigators have isolated and characterized genes that cause or predispose patients to cystic fibrosis and many metabolic disorders; several neurological diseases, including Huntington's disease and some forms of Alzheimer's disease; and cancers of the breast, colon, kidney, and other tissues. These discoveries are paving the way to: (i) the more widespread use of genetic testing, to assess the risk of future disease, as well as to diagnose disease; (ii) the development of methods to introduce genes into appropriate cells to treat both acquired and inherited illnesses ("gene therapy"); and (iii) the design of new strategies against disease based upon a more profound understanding of the mechanisms that cause disease.

—The advent of molecular cloning and the dramatic growth of the biotechnology industry have already produced several extremely valuable clinical tools. These include bacterially-produced hormones, such as human growth factor, that offer advantages of safety and expense; blood growth factors, such as erythropoietin and granulocyte and platelet stimulants, that can reverse bone marrow failure and shorten hospital stays for patients with cancer, AIDS, and kidney disease; and new vaccines for hepatitis B virus and others.

—New methods for determining protein structures and the interactions of proteins with other molecules are reshaping approaches to the development of new

pharmaceuticals. For example, the cocaine receptor, a protein that transports dopamine into cells, has been found to interact with cocaine and dopamine at different sites, suggesting new ideas for medications against cocaine addiction.

—The recent isolation of genes from mice, rats, and humans that regulate appetite and energy utilization and cause obesity and diabetes has revolutionized approaches to these common medical conditions. The genes govern an unexpected hormonal circuit dominated by the hormone called "leptin" that is produced by fat cells and responded to by the brain. New pharmaceutical products that interfere with this circuit are likely to become important agents in the control of obesity and its complications.

CLINICAL RESEARCH IN TRANSITION

A healthy biomedical research enterprise requires financial support, excellent facilities and equipment, and talented personnel for a wide range of activities, from fundamental laboratory research to clinical trials. Only in this way can discoveries in the laboratory be converted to health benefits for our citizens. Yet clinical research, both at the NIH and in the extramural community, is threatened by deteriorating physical facilities, inadequate recruitment and training of patient-oriented investigators, and declining populations of clinical subjects. The increasing dominance of managed care networks, with their emphasis on cost control, further challenges research and teaching activities at the Nation's academic health centers, where most NIH-supported clinical investigation is conducted. We need to be prepared to respond to these trends if we wish to sustain the integrity of patient-oriented research programs at a time when advances in genetics and cell biology promise dramatic changes in the practice of medicine. During the past two years, I have worked closely with my colleagues in both the intramural and extramural communities to develop a plan to counter this nationwide erosion of clinical research. Our accomplishments and further strategies include:

—(1) Establishment of a Clinical Research Panel, chaired by Dr. David Nathan of the Dana Farber Cancer Center, to advise NIH on the funding of clinical research, the training of clinical investigators, and the revitalization of sites at which such research is done. The Panel and its subcommittees have been meeting and gathering information for nearly a year and are expected to deliver recommendations to the NIH Director's Advisory Committee this June.

—(2) Development and implementation of a pioneering core curriculum at the NIH to help prepare young physicians for careers as clinical investigators. The central feature of this curriculum is a course that runs throughout the academic year and consists of four modules. These modules introduce clinical fellows to important topics in clinical research, such as epidemiologic methods, ethical issues, monitoring and regulating patient-oriented research, and approaches for funding clinical research studies. We are making course materials available to interested investigators and training program directors across the country so that this program can serve as a model for other health centers. We are also now televising Clinical Center Grand Rounds via satellite to 100 academic hospitals around the U.S.

—(3) Establishment of a loan repayment program. Translating advances from frontiers in fundamental science to the bedside requires a cadre of highly skilled clinical researchers trained in both laboratory and clinical research methods. However, just when the scientific opportunities beckon talented physicians, we have seen a serious decline in the numbers of trainees entering and completing clinical research training. Part of the reason for this decline is the burden of debt from earlier education. The median debt for medical graduates in 1995 was $65,000, and debt is often $100,000. Students may well conclude that this level of debt is incompatible with pursuit of an academic career. For this reason, approximately a year and a half ago, the NIH established a loan repayment program in clinical research for physicians from poor and disadvantaged backgrounds. We are just now beginning to reap the fruits of that investment. Nineteen physicians currently enrolled in clinical research training on the NIH campus are receiving repayments of their educational loans at $20,000 per year.

—(4) Reexamination of the review of clinical research proposals. Two years ago, a panel of scientists from academic institutions examined the fate of clinical research grant applications at NIH and recommended significant changes in the review process for these grants. Once a new director is selected for the NIH Division of Research Grants, an initial task will be to find innovative ways to implement some of these recommended changes in peer review.

—(5) Improved monitoring of NIH-funded and conducted clinical trials. Last summer, the NIH Office of Extramural Research evaluated clinical trials supported

and conducted by the NIH Institutes, Centers, and Divisions in order to optimize mechanisms for oversight of these trials. These findings will be further considered by the Clinical Research Panel.

—(6) Negotiated agreements for reimbursement for participants in clinical trials. Last month, the National Cancer Institute (NCI) signed an important agreement with the Department of Defense that will permit members of the armed forces and their dependents to enroll in NCI clinical trials under the CHAMPUS health care system. This could become a model for reimbursement by other health care providers and insurers for experimental treatments for many diseases and help to reverse the trend that is drawing patients away from research projects into forms of care thought to be less costly.

—(7) Construction of a new NIH Clinical Research Center. In the fiscal year 1997 budget for NIH, the President requests a total of $310 million to replace the existing 43-year old NIH Clinical Center, much of which is now functionally obsolete, inefficient and potentially unsafe to operate, and expensive to maintain. The Clinical Center houses nearly half of all federally-funded clinical research beds in the country and accounts for one-fourth of all federally-funded outpatient clinical research visits. These patients account for approximately 65,000 inpatient days and 70,000 outpatient visits for experimental treatment and for the study of frequently occurring as well as rare or "orphan" diseases.

—(8) Improved NIH Clinical Center operations. This year, the DHHS Secretary commissioned a review and report on options to improve the efficiency of Clinical Center operations. The review panel recommended changes in the governance, funding and management of the facility. Many of these changes are already being made, but others can be fully implemented only when the new Clinical Research Center is in operation.

—(9) Increased clinical collaboration with physician-scientists in academic health centers. NIH intramural scientists are already collaborating with extramural scientists on clinical projects, for example through sabbaticals at the Clinical Center, via telemedicine, and through programs that provide one-day-a-week use of the facility for extramural researchers. Once the new 250-bed Clinical Research Center with its associated laboratories is completed, extramural-intramural collaborations will increase, thereby strengthening both intramural NIH and the Nation's overall medical research enterprise.

ECONOMIC BENEFITS OF NIH-SPONSORED RESEARCH

NIH-funded discoveries not only improve the Nation's health, but also result in economic benefits to the nation and the individual. NIH research helps support skilled jobs both at academic institutions and in the many U.S. companies that provide materials and instruments used in research. Many of the successes in the biotechnology and pharmaceutical industries are related to NIH support of clinical and laboratory research. In 1994, the 1,311 U.S. biotechnology firms employed 103,000 people and generated $11.2 billion in revenues. Recent research suggests a direct linkage between the presence of highly productive scientists, most of whom receive NIH support, and an increase in start-ups and the growth of new biotechnology companies. In addition, the top 15 U.S. pharmaceutical industries—whose work is based upon fundamental research funded by NIH for decades—employed more than 350,000 people and earned profits of $13.3 billion on sales of $84.8 billion.

NIH-supported research has also led to many "spin off" technologies including: agriculture (genetically altered plants and animals are improving yields and extending the shelf life of common foods); manufacturing (genetically-engineered enzymes are revolutionizing the production of many chemicals); and the environmental sciences (modified bacteria and biophysical methods are inexpensively restoring soil and water to their natural states following industrial contamination).

In some cases, medical research does not yield marketable products, but still contributes to public health and yields substantial cost savings. For example, NIH-funded research has demonstrated that weight training for the frail elderly reduces the risk of falls and the associated costs of hospitalization. By helping to create and sustain a healthy, productive population, NIH provides immeasurable benefits to the Nation.

Economic studies will increasingly be called upon to demonstrate how the Federal funds received by NIH significantly improve public health, enhance the productivity of health-related industries, and contribute more generally to the well-being of society and the Nation. For example, the development of laser-based photocoagulation treatment for early stage diabetic retinopathy can arrest impairment of vision at a later stage and has been estimated to save the Nation over $1 billion per year. The use of clozapine as maintenance treatment for schizophrenia reduces the need for

hospitalizations costing $1.4 billion per year. Estrogen replacement therapy lowers the rate of hip fractures among women aged 65 and older and is estimated to save $333 million per year.

CONCLUSION

For more than five decades, medical science supported by NIH has benefited from the unwavering support of our Nation's citizens and their leaders. The resolve to create and sustain a program of superlative medical research has yielded multiple benefits, including vast improvements in human health and well-being; significant contributions to the economy; and an extraordinary store of knowledge related to basic biologic mechanisms, the causes and course of disease, and innovative treatments.

The pace of progress in medical science is astoundingly rapid. But it is clear that the most critical scientific discoveries and the clinical applications of these discoveries still lie ahead. I believe the great potential for continued progress merits consistent Federal support for medical research.

I will be pleased to answer any questions you may have.

CLINICAL RESEARCH PANEL

Senator HATFIELD. Thank you very much, Dr. Varmus. As I indicated, your written statement will be placed in the record. You raise a number of issues in that and if you do not mind, I would like to pose a few questions to further elucidate.

I want to reaffirm the fact that for 2 to 2½ years, you have been very busy trying to counter the nationwide erosion of clinical research and, as you know, in 1994 there were two major reviews of the clinical research program that identified substantial areas of concern and issued several recommendations to immediately address the deficiencies.

I have met with Dr. Nathan, the chair of your new review. I suppose being in politics as long as I have been, my question is really based upon sort of a background in my culture. Why another review?

Dr. VARMUS. Well, Senator, let me try to answer that. First of all, I do not see this as a review. My view of Dr. Nathan's panel, actually it is my panel that he chairs, is that that panel is constituted to develop action items. We, of course, have paid very careful attention to the report from the Institute of Medicine. I even carry a copy with me. We are asking that Dr. Nathan and his colleagues look at the recommendations of that panel. But, we are not trying to redo the study. We are attempting to look at the recommendations and see which are most appropriate and which are most feasible to address now.

I would also point out that the IOM report was directed largely to the important issue of recruitment of scientists into clinically oriented research. Many of the other questions that we are concerned about—facilities, financial support—are only peripheral to some of the concerns in the IOM report. So there are some other issues that do need to be looked at.

I would take a very similar stance toward what I think is implied by the first statement in your question, that we had also in 1994 learned about Dr. Williams' report. Again, Dr. Nathan's panel has not been asked to look at how clinically oriented research fares in the peer review system. The committee is asked to make some recommendations that could be taken to the division of research grants to ameliorate a situation which we recognize is not perfect.

In my view the most important thing that has been uncovered in the Williams report on peer review was that there were a substantial number of applications for patient-oriented research that were being reviewed by study sections that saw less than 30 percent clinical research applications. We are making a concerted effort to be sure that that does not happen.

Senator HATFIELD. In other words, they are not starting from scratch but they are reviewing some of the recommendations that have not been implemented from those previous recommendations.

Dr. VARMUS. Well, I would say very few of the recommendations have been implemented. There are some concerns that have de facto been eased somewhat. For example, the number of trainees who were in loan deferment programs or in clinical investigator awardships has increased, not necessarily in response to the report, because some of these things were happening before the report was issued.

But we are following those trends and looking for things that were in the IOM report to ensure that everything that is good in it is implemented. We had a member of the report panel come and speak to Dr. Nathan's panel at its first meeting, and we are trying to link our own actions to the recommendations of the report.

## LOAN REPAYMENT PROGRAM

Senator HATFIELD. Let me turn a moment to the 1994 congressional authorization relating to the NIH loan repayment program for individuals who are involved in clinical research. As I understand it, the basic limitation has been placed on those physicians from poor and disadvantaged backgrounds involved with the NIH intramural program.

As you know, the bill that I am offering this time does expand the eligibility from programs including physician scientists with heavy debt burdens in both the intramural and extramural communities.

Does NIH have authority to expand this program, under the current legislation or do you feel it is necessary to restate that at a legislative forum in this bill?

Dr. VARMUS. Senator, we do not have the authority at this point to do that. We would like to be able to do it. We have asked for that to be included in the current reauthorization bill. I am sure you know that Senator Kassebaum has held a hearing to discuss our revitalization act, although at the time of our hearing we were not able to be explicit about the legislative proposals we are endorsing because they had not yet been cleared by OMB. It is now the case, and we can say publicly that we are asking for those authorities.

Senator HATFIELD. When you referred to the peer review system, you say that you do not have specific implementation from the previous report, but that it is happening anyway.

Dr. VARMUS. Some things are happening in response to the report and some——

Senator HATFIELD. Is it working?

Dr. VARMUS. Well, I think that is a very important question. In fact, one of the difficulties we chronically have at NIH is knowing what is happening. For example, many of our investigators are

training on what is called a KO8 award, a clinical investigator award. These are largely graduates of medical school who are participating in various kinds of biomedical research training programs. We do not know exactly how many of those are learning to do patient-oriented research. That is a concern that we are trying to address.

As you know, it has been very difficult to determine how much the NIH spends on clinical research because the definitions have never been terribly clear. My new panel has wrestled with this question—a question which was raised by, but not answered by, the IOM report. We decided that rather than try to figure out what has happened in the past, we should use a definition that we all now accept for patient-oriented research and look over the course of the next year at the amount of money that is going to a more clearly defined set of research projects that address clinical issues. I think we will know within a year or two how much is being spent on real clinical research training and on clinical research activities.

COLLABORATION WITH OTHER AGENCIES

Senator HATFIELD. Another place in your testimony, you have said it in your summary, you mentioned the National Cancer Institute's unique partnership with the Department of Defense relating to reimbursement for those members of the Department who participate in clinical trials.

Do you anticipate that that can be expanded beyond the disease of cancer and, No. 2, have you had any discussions with Donna Shalala over at the HHS on the possibility of finding a system to cover Medicaid and Medicare programs?

Dr. VARMUS. Well, the answer to both those questions, Senator, is yes. In the case of the diseases, yes, we have been talking with other institutes about trying to develop similar initiatives. We have been having conversations, not only with Donna Shalala but also directly with the Administrator of HCFA, Dr. Bruce Vladek. Coincidentally, just yesterday he came out to NIH to talk to me and to Dr. Klausner and Dr. Lenfant about some of these issues. I think we are making real progress. We are also having conversations with the Veterans Administration. I think there are many ways in which we can also address insurance companies and managed care companies. I think there is a lot of goodwill in this area.

Right now as we enter this fairly ferocious battle for dominance in the dramatically changing health care market, there is a great deal of attention to short-range issues. We are hoping the project carried out by the DOD and the NCI will demonstrate that clinical research can be conducted with little or no increased costs, especially in the area of clinical trials. That will be an inducement to have more folks support the clinical expenses of some of these protocols.

CLINICAL RESEARCH PANEL

Senator HATFIELD. Again on page 8, you refer to your panel headed by Dr. Nathan at the Dana Farber Cancer Center. Is there a time line on this report and will it dissolve, will the panel dis-

solve, after the report, after it issues its findings or recommendations?

Dr. VARMUS. Well, let me emphasize again, Senator, that I am not asking this panel to deliver a report. I am asking them to recommend action to me on a variety of topics. I have asked them to be empaneled for 3 years. At the end of that 3-year period we will evaluate what to do next.

Quite frankly, one of the additional reasons I put this panel together was my concern that we needed a way to respond to emergencies in clinical research. When I came to NIH we had just had a very unfortunate episode in which a number of patients died as a result of a clinical trial in which a drug called FIAU had been used.

I felt I needed then a body of distinguished clinical investigators to whom I could turn for help in such an event. Whether I need a standing body of that kind is something I will determine after I have had them in place for the 3 years, but I expect them to be——

Senator HATFIELD. How old is the panel now?

Dr. VARMUS. About a year.

Senator HATFIELD. About a year. So 2 more years.

Dr. VARMUS. That is right. They have been coming to my advisory committee meetings, and they will continue to do so. I expect them to have actually a number of reports that will be intended, not so much to tell me that something is wrong, as to tell me what to do.

Senator HATFIELD. So those will be recommendations.

Dr. VARMUS. They will be firm recommendations.

Senator HATFIELD. And will they be then peer reviewed or will they——

Dr. VARMUS. Oh, no, no. Senator, I have a track record I'm willing to stand on for taking action.

Senator HATFIELD. Good. Good.

Dr. VARMUS. We will take action.

## GOVERNMENTWIDE CLINICAL RESEARCH

Senator HATFIELD. As you know, in my bill there is a President's clinical research panel as a part of the science and technology department, and you will recall we had previous conversations when that was undertaken under this administration where we found there were no life scientists on that particular science panel and we made inquiry and one was then appointed.

My question is, basically, that I would like to know your opinion on having the clinical research panel as a part of the White House Presidential Office of Technology, not to duplicate responsibilities within the NIH, but to provide a forum to examine the clinical research which cuts across so many Federal departments, as you know, and whose jurisdiction falls outside the mission of the NIH.

So if you would care to comment or if you think we should word it in a better way, we are open to suggestions.

Dr. VARMUS. Well, Senator, we are out here in Oregon. One thing I have learned in Washington is that oversight groups work best when they are close to the action. They are respected, they are better informed, and they are closer to the events they are trying to oversee. So my own view is that if you want to have an influence

upon clinical research activities, you put the panel at NIH where the vast majority of clinical research is done.

We have people on the existing panel who are involved in many other kinds of clinical research activities. We have representatives of the pharmaceutical industry, the insurance industry, the academic health centers, and the other elements in the Government that have significant roles in clinical research. So I think that there is an opportunity within the existing panel to provide all the activities that you seek with your panel at a higher level in Government.

Senator HATFIELD. If it were located in the NIH, would it be an asset or a liability to you?

Dr. VARMUS. Well, I think what you would then have is basically what we have in the Nathan panel.

Senator HATFIELD. We would have a continuation. That is why I asked you first about the Nathan panel because if it dissolves, then we have lost that kind of focus. It seems to me that following recommendations and the implementation of recommendations is always good to see the reaction response to the panel that has created the recommendations, but if they have dissolved and gone home, so to speak, I would not argue the case as to where it should be located as much as the existence of one.

Dr. VARMUS. My view is that the panels will be making recommendations and seeing action long before they are dissolved. My bias has always been to see how things work before I make them perpetual.

Senator HATFIELD. When do you expect those recommendations?

Dr. VARMUS. Some in June.

Senator HATFIELD. This coming June?

Dr. VARMUS. Yes.

Senator HATFIELD. Thank you very much. I will submit some further questions to you, Dr. Varmus, for the record. We are most grateful for your presence and for enhancing the hearing by your testimony. We appreciate it very much. I want to thank you too for the lecture you are delivering here on the campus a little bit later this afternoon. I hope to be finished by then, but if I am not, I will get the reviews. Thank you very much, sir.

## NONDEPARTMENTAL WITNESSES

### STATEMENT OF DR. PETER KOHLER, PRESIDENT, OREGON HEALTH SCIENCES UNIVERSITY

### ACCOMPANIED BY DR. LYNN LORIAUX, CHIEF OF MEDICINE, OREGON HEALTH SCIENCES UNIVERSITY

SUMMARY STATEMENT OF DR. PETER KOHLER

Senator HATFIELD. The second panel is Dr. Kohler, the president of Oregon Health Sciences University. Dr. Lynn Loriaux, the chief of medicine at Oregon Health Sciences University. Dr. Monica Farley from Emory University representing American Federation of Clinical Research, and Dr. Gordon Williams, of Brigham and Women's Hospital, Boston, MA.

Lady and gentlemen, we proceed here on a very informal basis and you may read your statement, or your statement will be placed in the record, or you may summarize or highlight, do anything you want to. We are just happy to have you here. Thank you for coming, particularly for our out-of-town guests, Dr. Farley and Dr. Williams.

Dr. KOHLER. Thank you. I will be glad to lead off and abandon my written comments, which I understand will be in the record, and just to say, first of all, thank you for having this hearing here. I think the subject being addressed is critically important to all of us in this country. And I look at this from a perspective from an old or prior, I guess I should not use the term "old," clinical researcher and also someone who heads up an academic health center that is striving for excellence in the area of research and very concerned about some of the issues that you have pointed out.

Clearly you and others have identified problems: The major drop in the number of applications for young investigators; where is the new blood going to come from in research; the 70-percent decrease in Federal grants to people under 36 years of age; too few minorities in the research endeavor; and something that I think is perhaps under appreciated, the huge debt load that is carried now, particularly by medical graduates in this country when they finish graduation, which I think is a real deterrent to looking at a research career with debts in excess of $60,000 to $100,000 to pay off.

In years gone by, I think clinical research seemed easier to do. There was frankly less sophistication many times with regard to the clinical problems being addressed. There was a lot to be done in terms of making diagnosis and treatment. And one of the things from which I think the country has benefited in an amazing way in the past frankly was the doctor draft in the 1950's and 1960's that gave NIH at the clinical center literally the choice of the brightest students graduating in the country. They would go there.

I felt very fortunate to be selected with a rather strange background to go to NIH, but I learned research there, participated, and it has been amazing to note that the academic institutions of this country have been populated with people who passed through NIH in the 1950's and 1960's. When the doctor draft stopped, NIH still had access to very bright investigators of all types and I think the influx of M.D.'s perhaps slowed down appreciably, although there was still a very strong influence of the Ph.D.'s who were recruited to NIH at that time. And, of course, the program there has done extremely well.

I think, though, that as we have looked at the evolution of research in this country, the environment appears to be more hostile or less friendly, shall I say, to people in the clinical research area. It has been an uncertain career choice for a lot of individuals for reasons that you have outlined and I think understood by everybody and that young M.D.'s just finishing their training either may not be trained in research adequately or may choose not to go to this career because they are just not sure they can sustain it in the future.

But I think the problem of attracting bright young physicians and other clinicians into research is an extremely important one addressed by your bill. There are great potentials now, even in the very sophisticated areas of research. There are a couple going on on this particular campus that I think are worth pointing out. In the area of Fanconi's anemia, there is gene research going on that needs to be or will need to be tested here or elsewhere in humans. I think also there are some exciting things in the area of the neurosciences occurring.

This gives an increased complexity to the treatment if you have to put it into a specific target organ as difficult to reach as the brain and the nervous system, but, in fact, the studies by Dr. Newelt, for example, on the model for Sandhoff's disease I think are very important, ultimately to human disease.

But we do need a more supportive environment for clinical researchers. Training opportunities are necessary, as you pointed out, and I would like to say that these opportunities really do not all need to be at the clinical center of NIH. Even as an alumnus of that institution, I think we have, for example, on this campus a new building that will specifically be designed to house clinical research studies that are externally funded and I think it is going to be very important for us and other academic health centers to continue to carry out clinical research programs here, and it is certainly my belief that we can participate in the training of clinical researchers in the future. So our care building, we think, can be an example. It was, in fact, modeled in many ways after the clinical center at NIH for the carrying out of clinical research in academic health centers.

One point that I would like to emphasize that I think is important for all of us to say again and again is research really does have the potential to lower the cost of health care in the future and I know that has been a particular interest of yours, Senator Hatfield. Research sometimes has a bad name right now and it is because of, I guess, what Lewis Thomas has called the halfway technologies that seem to add on to the cost of health care without nec-

essarily leading to cures, but I do believe that cures will be found through combinations of molecular techniques and clinical research and we should focus on that in the future.

So I certainly believe that while NIH has begun to take many important steps under Dr. Varmus, your Senate bill 1534 should really help us deliver on the promise to the citizens of this State and this country.

I would like to close with a quote from our chairman of neurology, Dr. Earl Zimmerman, who wrote recently when he learned you were coming: "* * * that it seems almost ironic that the academic research enterprise in this country seems about to fail when the opportunities are so wonderful." This is particularly true—now remember this comes from the chairman of neurology in the area of neuroscience—where just about every day some new treatment and insight seems at hand for diseases like Alzheimer's, stroke, Parkinson's, multiple sclerosis, and muscular dystrophy.

PREPARED STATEMENT

Let me just close by saying that I think academic health centers really are a great resource to this country. Over the last several decades they have been put together with joint fundings which has included the States, private enterprise, and certainly the Federal Government, and I think they can certainly play a major role in research and I thank you for the opportunity to come here today.

Senator HATFIELD. Thank you very much. I will be waiting until each panel has made their presentation before engaging in questions.

[The statement follows:]

PREPARED STATEMENT OF PETER O. KOHLER, M.D., PRESIDENT, OREGON HEALTH SCIENCES UNIVERSITY

Senator Hatfield and Members of the Committee, thank you for the opportunity to testify today about clinical research funding issues and the implications for academic health centers. It is a pleasure to welcome you, National Institutes of Health Director Harold E. Varmus and the other distinguished witnesses and hearing participants to our campus.

As the Chairman is aware, Oregon Health Sciences University is Oregon's only academic health sciences center [AHC]. As with most AHC's, our mission is multifaceted. We are an educational institution, training more than 2,600 physicians, dentists, nurses and allied health providers each year. We are a provider of last resort: each year millions of dollars of care is provided through our hospitals and clinics to Oregonians who cannot afford to pay for that care. We are a community resource, providing outreach services that range from oral hygiene screenings and drug and alcohol abuse counseling for pregnant women to a 24-hour poison information line and assistance to the local school district in its efforts to establish a health high school in the metropolitan area.

We are also a major employer and economic engine for our city and state: our employee base of more than 8,000 makes OHSU Portland's largest employer and Oregon's seventh largest. The institution is a revenue producer for the state, bringing in more than $150 million in out-of-state dollars each year and creating tens of thousands of jobs in related industries.

Our last major role, and the one I will be focusing on today, is in the area of research. In terms of size and dollar amounts OHSU is the major locus for biomedical research in this state. The university currently is home to $200 million in ongoing research projects. Last year we received competitive NIH awards totaling $46.3 million. Overall, our research volume ranks 60th out of 2,000 research universities.

On its face, this funding level would appear to be cause for celebration. In many ways it is. Just 10 years ago, our NIH awards totaled only $9.7 million per year. Our phenomenal growth since that time has been thanks in no small part to the outstanding investigators who have joined us here in the Vollum Institute for Ad-

vanced Biomedical Research and our other research institutes and departments. While neuroscience has been a particular focus for OHSU, investigators here also are making significant contributions in the areas of gene analysis, cancer, movement and sleep disorders, and dietary issues, just to name a few.

OHSU scientists have discovered new ways to cross the blood-brain barrier to deliver important cancer-fighting drugs to tumors in the brain, identified the key role melatonin plays in regulating sleep-wake cycles, and initiated important new drug and surgical strategies for ameliorating movement disorders related to Parkinson's and other neurological diseases. Gene research underway at OHSU holds promise of developing a cure for Fanconi's anemia. Critical work also is underway in the areas of treatment of stroke, causes and treatment of mental illness and substance abuse, HIV pathogenesis, development of better anti-rejection drugs for transplant patients and development of cholesterol reducing drugs, among others.

OHSU researchers also are bringing their achievements to market. As of last year, OHSU investigators had made 237 invention disclosures, many of which were licensed to biotechnology and pharmaceutical firms. Four new companies have grown out of OHSU faculty discoveries and a fifth such company is in the planning stages.

When I came to this campus eight years ago, one of my stated goals was for OHSU to become one of the top 20 research institutions in this country. That is still my goal and the goal of our campus, but it is an increasingly challenging one. Although the research volume at OHSU has grown impressively over the past 10 years, the rate of growth has slowed in the last year. Our investigators, like their counterparts nationwide, are finding it harder and harder to win awards, particularly on the first application. This is particularly true for junior scientists, but even the more-established senior investigators are finding funding increasingly difficult to obtain.

The reasons are well known. After decades of unwavering support, funding for the National Institutes of Health and other research programs has come under attack on Capitol Hill. Proposals have been made for major cuts, and while the most serious measures have not been approved, NIH funding has increased only minimally and may well begin to fall. The number of biomedical researchers, meanwhile, has increased faster than available funding, placing greater demand on NIH. The result has been a more competitive selection process and one which critics claim too often overlooks the potential merit of new proposals from young, unproven investigators in favor of those that come from more established scientists or involve ongoing projects.

The private sector picture is only somewhat better. While research expenditures by pharmaceutical manufacturers, biotechnology companies, health maintenance organizations and other private enterprises have increased, academic health centers are not necessarily the beneficiaries. For-profit drug testing centers are being set up with a mission of providing fast, low-cost results, but these are unlikely settings for the emergence of major new breakthroughs. And biotechnology firms are not filling in the gaps as some may have hoped. Although many of them are collaborating with universities to some degree, the vast majority of their resources and research is headed in-house for financial and other reasons.

Managed care, with its emphasis on squeezing every "excess" dollar from the system, may ultimately place the greatest strain on AHCs. Not only are the plans looking for least-cost, often non-AHC settings in which to conduct their own clinical projects, they also are siphoning off federal funds previously used to fund medical education and research. Dollars which, under the fee-for-service model, were used to fund graduate medical education are now being distributed evenly throughout the system. For the HMOs, which often provide neither much training nor any indigent care, this represents an inappropriate windfall. For AHC's, it is the loss of yet another critical funding source.

The reduction in patient volumes at AHC's which has resulted from the shift to managed care, is another blow to AHCs' ability to survive and to conduct important research. A sufficient patient volume not only is key to training providers, but to conducting clinical research. Some speculate that the pressure on faculty to produce more clinical revenues may also be having a negative effect on research as more energy and time is expended on patient care tasks.

For a former NIH investigator and an academician this is a painful process to watch. Working in concert, the public and private sectors have built a powerful biomedical research enterprise in this country over the past 50 years. The financial investment in this enterprise has been significant, but so have the returns. Childhood cancers that would have meant an immediate death sentence 30 years ago are now curable. AZT is being used successfully to prevent transmission of HIV from infected women to newborns. Laser treatments have been discovered that can prevent blind-

ness in persons with diabetic retinopathy. Warfarin and aspirin are being used to reduce by 50 to 80 percent the risk of stroke in individuals with atrial fibrillation.

Despite these health care successes and the many others like them, some critics argue that the cost of research outstrips its benefit to society. This ignores the enormous potential for both basic and applied research to effect cures and lower the threat of diseases affecting either large or small populations. To the extent that research adds to the cost of health care, it is generally in the area of instrumentation, or what Lewis Thomas has called "halfway technologies." Even in those cases this does not suggest a need to abandon research, but rather the importance of taking the research to the next level where the testing or treatment is both efficacious and cost-effective. The new emphasis on health outcomes research is important to achieving this latter goal.

When one talks about the importance of biomedical research and the need to maintain and build on the biomedical research infrastructure erected in this country over the past half-century, one is necessarily talking about academic health centers. While not all medical breakthroughs have occurred at the AHC's, these institutions undeniably have been at the heart of the biomedical research enterprise. Because of their multifaceted role as educational, health care and research institutions, AHC's have served as the breeding ground for discoveries which can be taken from the bench to the bedside. Their chief partner in this effort has been the NIH, which has served not only as a funding resource but, perhaps most importantly, as the major source of talent to drive the clinical research engine.

During the doctor draft and the Berry Plan in the 1950's and 1960's, NIH had its pick of the best and brightest medical school graduates in the country. These young physicians came to NIH as research and clinical associates, learned research and, over the past few decades, became the backbone of academic faculties. Now, however, we appear to be at a crossroads. While the stream of extremely bright clinical investigators into and out of the NIH has continued, it has also slowed.

A confounding factor is that young clinical faculty find it increasingly difficult to obtain NIH funds to support independent research. The combination of the lack of financial support today, concerns about what sort of support will be available in the future and the pressures of today's clinical environment are having a chilling affect on our ability to attract the next generation of the best and brightest to research careers.

While there are no easy solutions to these problems, certainly the Clinical Research Enhancement Act of 1996, introduced by the Chairman, is an important step forward. By establishing a Clinical Research Panel at the Presidential level, creating mechanisms that will help NIH study sections to be more supportive of clinical research and providing increased funding for clinical researchers and the Clinical Research Centers program, the proposed legislation addresses some of the key problems we face. I am especially pleased to see the emphasis in this bill on increasing the number of First Awards as a way to encourage the next generation of scientists and ensure that they will be around to build on the successes of the previous generation.

I would like to end my testimony by repeating a comment made to me by our Chair of the Department of Neurology, Earl Zimmerman, when he learned I had been asked to testify here today. Dr. Zimmerman said, and I quote: "It seems almost ironic that the academic research enterprise in clinical research is about to fail us when the opportunities are so wonderful. This is particularly true in neuroscience disease when just about every day some new insight and new treatment seems at hand in Alzheimer's, stroke, Parkinson's Disease, Multiple Sclerosis, etc."

While I hope Earl is not a prognosticator and the academic research enterprise will not fail us, I share his sentiment that it is a shame even to see it falter at such a critical time for gene therapy, neuroscientific endeavors, and other key research areas. I believe we can and should do more to enhance the health of our citizens. I also believe that we can and should place a priority on funding clinical research and the training of adequate numbers of clinical researchers.

Society, the states and the federal government through NIH have invested a great deal in building the AHC research infrastructure. In return society has received highly educated providers and the potential for treatments and/or cures for a variety of devastating health conditions. We should build on these accomplishments, not tear them down. Working together I trust we can.

Thank you again for the opportunity to testify. I would be glad to answer any questions.

SUMMARY STATEMENT OF DR. LYNN LORIAUX

Senator HATFIELD. Dr. Loriaux.

Dr. LORIAUX. Thank you, Senator Hatfield, for inviting me to speak to this panel. I thought in contrast to Peter, who is a better extraneous speaker than I, I would perhaps stick to my notes a little more closely than he was. I was looking over his shoulder and I am amazed what he left out there. In fact, I could use that third point there. Hand it over. [Laughter.]

But in preparing these notes, I only had 5 minutes to speak, I was reminded of what Winston Churchill once said in a letter for a friend. He said, "I am very sorry for writing this long letter but I didn't have time to write a short one." I did take the time to write a short one, and so I thought I might take advantage of it and read it.

What I have tried to do in this little exposition is kind of trace the history of the importance of clinical investigation in American medicine and to American medical centers, academic medical centers, and then try to illustrate what I think has gone wrong, and I do that pretty much from my own experience. I have been an aspirant to the discipline of clinical investigation and a participant.

I spent 20 years where Dr. Varmus now is at the NIH doing that very thing. At one time I tried to manage it. I was a manager of clinical investigators and clinical research and now I manage the managers, and although clinical investigation as a primary activity is a mere vestige in my life of what it used to be, I still am quite passionately attached to it and very concerned about its welfare.

With that being said, let me just read here what I have written. Medicine in America was reasonably undistinguished until the early years of this century, when academic medical centers began to provide full-time positions for medical scientists and an expectation of employment, which was excellence in teaching, practice, and research.

American medical graduates were sent to the great medical centers of Europe to experience firsthand the best things available and came back with a clearer understanding of the scientific habit of mind and its application to problems of health and disease. This combination and a generous philanthropy of the time really together catapulted American medicine into the lead where it has really remained, essentially undisturbed, until the present time.

In the last 50 years, it is, in fact, been the young physicians of Europe and Asia that find their way to our academic medical centers to seek out our secrets of success. In that sense, the people of America and the world are really the immediate beneficiaries of all this good fortune and success.

I think there are several factors that play central roles in this success story: Public moneys currently from the NIH, but formerly from philanthropic organizations; I think the geographic full-time system of academic employment are two of the most important. Both of these things are now under siege and you know full well about the budgetary wars having to do with the NIH appropriation.

Nonetheless, given the importance of these two things, I think the centerpiece of our success has been the clinical investigator. This person is usually a full-time employee of an academic medical center and focused full energy on solving problems of human pathophysiology. It is important to realize that these investigators never relinquished patient contact and for the most part moved

with the facility between the laboratory and the clinic bringing the synergy of both of these worlds to bear on the chosen research problem.

These people were known in the old days as triple threats. These are experts in teaching patient care and research. These were the role models for my generation of physicians and indeed exemplified our highest professional aspiration. It seemed then to me and still actually does today to be a life worth the sacrifice and a life of substantial satisfaction and a life in which the possibility of real contributions to mankind was ever present.

In 1974, as Peter has just pointed out, coincident with the end of the draft there was an acute and alarming change in the number of NIH applications for physician scientists, which is in contrast for those applications for, Ph.D., scientists, which continued to rise. I think that this trend has continued. I do not know whether that data has been reanalyzed recently, but it was in the late 1980's and if we believe what Yogi Barra says, "that you can observe a lot just by watching," I think that this is still a problem today. And I think as a consequence of this shift in demographics, the membership on study sections, the gatekeepers of research funding, has changed in parallel. This is an important observation.

In the mid 1970's if you went to a study section, it was composed primarily of M.D. scientists and there were a few token, Ph.D.'s. Today I think the reverse is usually true and I know this is an oversimplification of the problem, but in broad strokes I believe it to be correct and I think a visit to almost any sitting study section will confirm this observation. This demographic shift has led to a consequent shift in emphasis in funding from clinical to laboratory-focused research. This would be expected to occur and I think that that remains the situation today.

The consequences of this seemingly innocent change, indeed a change associated with unparalleled scientific growth and success, has, in fact, been devastating for clinical science. The most important effect has been the pressure to move away from patient-linked research into laboratory-based research for the clinical investigator to better fit the perceived, rightly or wrongly, biases of the study sections.

In order to compete with full-time scientists, it is usually, Ph.D., scientists with no clinical responsibilities, often with light teaching loads. The erstwhile clinical investigator has had to sever ties with two prongs of the triple threat, teaching and patient care, in order to achieve any measure of success in the grant world. It is not uncommon now to hear that the triple threat is a thing of the past and will never exist again.

Needless to say, this is devastating to the morale of those remaining in this career path, and is devastating to any hoped-for recruitment into this discipline. These changes have energized a slow downward spiral in the number of novitiates to our discipline and, in the final analysis, in its critical mass. It is difficult to find the bona-fide clinical investigator today.

In my own specialty of endocrinology, I think we have 1,500 academics scattered across the land. The number actually engaged in clinical investigation as previously defined can be counted really on the fingers of two hands. Where have these people gone? Where are

they now? They have gone into practice. They have gone into the refuge of industry-sponsored drug and device studies. Many have opted for early retirement.

Well, if this is all true and all this is happening, what are the consequences of this change? My belief and the most nefarious consequence is that academic medical centers are now developing two faculties, one clinical and one scientific. The result is a loss of relevance for the basic scientist and an attenuation of renewal by discovery for the clinicians.

Historically, it was the clinical investigator that knitted these two faculties together. Without them, basic science in academic medical centers can easily lose sight of the goals and missions of the host institution. For the clinical faculty, scholarship becomes a substitute for science. At a more visceral level, I think we are in jeopardy of losing our heroes in medicine, people who were our role models of the past and our pathfinders for the future.

What can be done? I think first must come the consensus that this activity is an important one and one that should be nurtured and supported, and I should add parenthetically from my current position as a department chairman, clinical investigators are a financial liability because they can rarely support themselves through grants and/or practice and in these times of austerity they are expendable.

The next challenge is to develop a mechanism of support for clinical investigation of a basic nature, and I am going to get into that in a minute with an overhead because I think this is a subtle but important nuance. We are not really talking about drug and device studies here. There is industry support for this kind of research and in many people's minds this is what clinical research is. Not in my mind. My mind is quite different from that. We need to develop some mechanism of support that will put clinical investigation back into as many academic medical centers as possible. That, of course, is the challenge and the object of this particular testimony.

One place to look that has not been mentioned yet is perhaps for-profit managed care organizations might share in the cost of discoveries that promote both profit and savings in their medical care operations. If a way is found, I believe that the tide will turn. Given some degree of security, I predict that the best students will again choose this career path.

There are other things that will help. Several have been already mentioned, debt forgiveness being among the most important. Many medical students have debts of greater than $100,000 or more upon the time of graduation and they really cannot contemplate any further financial insecurity. Focusing this program in the extant clinical research centers will have—I actually do not like the idea of centralizing this in one place close to the action. I think that the action is here, in all the medical schools in our country, and that is where the substrate for the future of this population of clinical investigators is going to come from. That is where we need the role models. That is where we need the examples.

I would like to focus these programs or the funding or whatever comes from this into the extant clinical research centers. This would have the added benefit of ensuring optimum utilization of

available clinical science laboratories, which is what clinical research really are, and at the same time it will build a cadre of users for the future, which is what these centers desperately need. I also think it would be good to devote some moneys to fund the experiences of medical students in this environment. This will highlight this career opportunity for many students who now have never seen or spoken to a clinical scientist in their entire medical school career.

So I think in the last analysis, America still produces two commodities that are everywhere known to be the best: Jet airplanes and physicians, and I think we are about to be reduced to one best thing. Many forces are arrayed against our system of medicine: A declining NIH budget, even though it has currently been somewhat reversed, much thanks for that due to you; managed care, which is a problem in the substrate, patient substrate, that we need for clinical research; rising anti-intellectualism in the land. I think that is a truism. And the loss of the clinical scientist. I do not think it is too late and I applaud your efforts to help us in this struggle.

If I could, I would like to show a couple of overheads, just to finish. If it is not completely out of order, I will ask the President if he could put this overhead on. [Laughter.]

What I want to try to do here is make this a more refined definition of clinical research and I sort of use this Latin square here to get at that. I think in my view there are poles. We can describe science in two ways. The one pole is applied science and the other pole is basic science and I think there are two kinds of participants in these activities. There are laboratory scientists and clinical scientists. Laboratory scientists pretty much confine their activity to the laboratory. We're all familiar with centrifuges, spectrophotometers and these sorts of things. Clinical scientists really have as their laboratory the clinic, the hospital, the clinical research center.

Now I would like to maybe point out some examples of these things. So an applied laboratory project, for example, might be the development of a biodegradable carton for hamburgers, a fast food thing. And this is something that is a challenging research problem, but it is one that has an immediate and profitable end in sight. The other extreme where basic laboratory activity might be the way in which the SRY protein, for example, bends DNA to determine a sex differentiation. It does not have any immediate apparent application. It is certain to have profound applications for the future, but nobody is going to fund that other than the public.

The same thing could be said for clinical investigation. An applied project might be finding the most appropriate dose of human growth hormone to ensure the best ultimate stature. That is something the pharmaceutical companies will pay for because it is going to immediately rebound to benefit them in terms of profit, unless an obvious project of a more basic nature might be trying to understand something like how insulin promotes salt retention.

There is no immediate reason to believe that this will be a profitable research endeavor unless it is found to have important clinical and ultimately industrial and pharmaceutical consequences. Now the key thing here is that this kind of activity can be funded by

industry, and this kind of activity, like clinical work, is funded by pharmaceutical companies almost exclusively.

This kind of activity, the laboratory basic science activity, is what the NIH funds for the most part. What we have lost is this funding down here. Who actually funds basic clinical research? That is what is gone away and that is what we are in the most need of restoring.

Now let me move to the next thing. What do clinical investigators do? That is the next little overhead, and I do not want this to be too simplistic, but I want to sort of draw a common definition so at least when we begin to discuss this we are looking at it from the same point of view. One of the things that has been lost in the clinical investigations is the ability to take advantage of the experiment of nature. This is the thing you can never get a grant for from NIH.

What happens here is a person with peculiar facies or peculiar stature or peculiar metabolism is found by a clinician somewhere and then deserve study, in depth, of a clinical point of view. That is what clinical investigators traditionally and in the future actually should do, at least in large part. And we cannot do that anymore. You cannot write a protocol to admit a patient like this, a single patient to a CRC. You cannot write a protocol to study this kind of single patient at the NIH. One time we could. In recent years, that has been lost.

So the way the clinical investigator functions is the whole cadre of clinicians over here are recognizing these experiments of nature. They are funneled into the bastion of the clinical investigator who actually defines and works out the clinical pathology which will point the way for understanding the molecular pathology, and at this point this is translated into the domain of laboratory scientists. Sometimes it is the same people; more often they are not. Often laboratory scientists working at the molecular level are nothing more than cells or skin or blood, plasma, that sort of thing, have been confused or labeled as clinical investigators when, in fact, they have missed the entire investigator human interaction.

On the other hand, many clinical investigators who have been struggling with this kind of problem have been viewed as inefficient or unproductive and clinical investigation has been labeled more as a device and drug trial kind of thing, which although scientifically valid, tends to be trivial and less profound in terms of what it is trying to achieve and its ultimate product.

The key issue here from a person like me as a department chairman is clinicians who are doing the recognition. Their salary is paid by third-party payors and they see their patients and they get their money. They make the salary. Laboratory scientists can take all this preliminary data and make wonderful grants out of that grant applications and actually apply for a good portion of their salary through the NIH or other funding agencies. There is nobody who is going to pay for this.

The CRC's will support the laboratory activities of the endeavor and is a place to put the patients, but how do we pay the investigator who needs to have unoccupied time in order to focus on the problem? If he makes his living seeing patients, he is not really doing this. If he makes his living getting grants, it is almost impos-

sible, actually, to do this. That is where the lesion lies and that is the thing, I think, that needs to be fixed.

So just to make a brief summary then, this is my conclusion from all of this thing. I think basic clinical science is a failing discipline. It is hard to find these people anymore. And the basic clinical science I am talking about is just as I have defined, people who are working on the same kind of fundamental problems using the human being as their model as laboratory scientists are using the human gene, for example, as its model.

PREPARED STATEMENT

And I think the primary reason for this is funding. There is no money to support these people anymore and this leads to unbelievable uncertainty and poor morale and when you have uncertainty and poor morale in a discipline, nobody is going to go there to work and are not going to commit their life to this kind of a career.

So I think it boils down to this thing. If this discipline is to be saved, which I believe it must, some new funding mechanism needs to be developed. So that is the end of my few comments and I thank you for the opportunity to say them.

[The statement follows:]

PREPARED STATEMENT OF D. LYNN LORIAUX, M.D., PH.D., CHAIRMAN, DEPARTMENT OF MEDICINE AND PRESIDENT, THE ENDOCRINE SOCIETY

Senator Hatfield and members of the committee, thank you for the opportunity to address with you the critical state of clinical investigation in American medicine.

Medicine in America was reasonably undistinguished until the early years of this century, when academic medical centers began to provide full time positions for medical scientists and an expectation of employment was excellence in teaching, practice, and research. American medical graduates were sent to the great medical centers of Europe to experience first hand "the best available" and came back with a clearer understanding of the scientific habit of mind and its application to problems of health and disease. This combination and a generous philanthropy of the time catapulted American medicine into the lead where it has remained, essentially undisturbed, until the present. In the last 50 years, it is the young physicians of Europe and Asia that find their way to our academic medical centers to seek out the secrets of success. The people of America and of the world are the immediate beneficiaries of our good fortune and success.

Several factors played central roles in this success story. Public monies (NIH), and the "geographic full time system" of academic employment are two of the most important. Both are now under siege. The centerpiece of this success, however, was the clinical investigator. This person, usually a full-time employee of an academic medical center, focused full energy on solving problems of human pathophysiology. These investigators never relinquished patient contact, and, for the most part, moved with facility between the laboratory and the clinic bringing the synergy of both worlds to bear on the chosen research problem. These people were known as "triple threats": experts in teaching, patient care, and research. These were the role models for my generation of physicians and, indeed, exemplified our highest professional aspiration. It seemed then, and still does today, to be a life worth the sacrifice, a life of substantial satisfaction, and a life in which the possibility of real contributions to mankind was ever present.

In 1974, coincident with the end of the draft, an acute and alarming change in the number of NIH applications from physician scientists (in contrast to Ph.D. scientists) was observed. This has continued, unabated, to the present day. As a consequence of this shift in demographics, the membership on study sections, the "gate keepers" of research funding, has changed in parallel. In the mid 70's, study sections were composed primarily of M.D. scientists with a few token Ph.D.'s. Today, the reverse is usually true. This is an oversimplification of the problem, to be sure, but in broad strokes, it is correct, and a visit to almost any sitting study section will confirm the observation. This demographic shift led to a consequent shift in em-

phasis in funding from clinical to laboratory focused research, and that remains the situation today.

The consequences of this seemingly innocent change, indeed a change associated with unparalleled scientific growth and success, has been devastating for clinical science. The most important effect has been the pressure to move away from patient-linked research into laboratory based research to better fit the perceived, rightly or wrongly, biases of the study sections. In order to compete with full time scientists (i.e., with no clinical responsibilities and often with light teaching loads) the erstwhile clinical investigator has had to sever ties with two prongs of the "triple threat" (teaching and patient care) to achieve any measure of success in the grant world. It is not uncommon to hear that the "triple threat" is a thing of the past and will never exist again. Needless to say, this is devastating to the morale of those remaining in this career path, and is devastating to any hoped for recruitment into the discipline. These changes have energized a slow downward spiral in the number of novitiates to the discipline and, in the final analysis, in critical mass. It is difficult to find a bona-fide clinical investigator today. In my specialty of endocrinology, with 1,500 academics scattered across the land, the number actually engaged in clinical investigation can be counted on the fingers of two hands. Where have these professionals gone? Into practice, or the refuge of industry-sponsored drug or device studies. Many have opted for early retirement.

What are the consequences of this change? The most nefarious is that AMC's develop two faculties, one clinical, and one scientific. The result is a loss of relevance for the basic scientists, and an attenuation of renewal by discovery for the clinicians. Historically, it was the clinical investigator that knitted these two faculties together. Without them, basic science in Academic Medical Centers can easily lose sight of the goals and missions of the host institution. For the clinical faculty, scholarship becomes a substitute for science. At a more visceral level, we are in jeopardy of losing our heroes in medicine, people who were our role models of the past, and our pathfinders of the future.

What can be done? First must come the consensus that this activity is important and should be supported. (Parenthetically, from the viewpoint of a Department Chairman, clinical investigators have become a financial liability because they rarely can support themselves through grants and practice and, in these times of austerity, are expendable.)

The next challenge is to develop a mechanism of support for clinical investigation of a basic nature (not drug and device trials * * * there is industry support for this kind of research)—that will put clinical investigation back into as many AMC's as possible. This challenge is the object of this testimony. Perhaps "for profit" managed care organizations should share in the cost of discoveries that promote both profit and savings in medical care. If a way is found, I believe the tide will turn. Given some degree of security, I predict that the best students will again choose this career path. Other things will also help—debt forgiveness being among the most important. Many medical students have debts of $100,000 or more upon graduation and cannot contemplate further financial insecurity. Focusing this program in the extant Clinical Research Centers will have the added benefit of ensuring optimum utilization of available clinical science laboratories and, at the same time, building a cadre of "users" for the future. Devoting some monies to fund experiences for medical students in this environment will highlight this career opportunity for many who, in today's medicine, have never seen or spoken to a clinical scientist.

In the last analysis, America still produces two commodities that are, everywhere, known to be the best: jet airplanes and physicians. We are about to be reduced to one best thing. Many forces are arrayed against our system of medicine; a declining NIH budget, managed care, a rising anti-intellectualism in the land, and the loss of the clinical scientist. It is, however, not too late, and I applaud your efforts to help us in this struggle.

Thank you for the opportunity to testify before this committee. I will be happy to answer any questions you might have.

**STATEMENT OF DR. MONICA FARLEY, EMORY UNIVERSITY, ON BEHALF OF THE AMERICAN FEDERATION OF CLINICAL RESEARCH**

Senator HATFIELD. Dr. Farley.

Dr. FARLEY. Thank you. Senator Hatfield, I would like to thank you for giving the American Federation for Clinical Research the opportunity to participate in this hearing. As you know, our organization is made up of approximately 12,000 physician scientists who do both basic science as well as patient-oriented research, and this

research is done at NIH as well importantly as at academic centers throughout this country.

We have followed with great interest and enthusiasm your efforts to bring attention to the crisis that confronts our Nation's clinical research effort, culminating in the introduction in January of S. 1534, the Clinical Research Enhancement Act. The problems confronting clinical researchers and their patients have received much attention but little action over recent decades. It seems to the AFCR that the problems confronting clinical research have been studied and then analyzed sufficiently. It is time for action and that is why the AFCR is so enthusiastic about your legislation.

Why is it so important to address the problems confronting clinical research? What is the impact of weakened clinical research effort? I think we have been hearing many of these issues raised and we will summarize our interpretation of them as well. First, improvements in patient care and the prevention of disease depend on clinical research, which translates basic science discoveries into tangible benefits of improved health. When clinical research is slowed, so is progress in medicine.

Second, the fruits of clinical research are often taken by industry, for example, and developed into new drugs, vaccines, and other health care products. These new products boost our economy and create jobs. Third, while not all medical discoveries reduce health care costs, many do as documented in NIH reports on the cost savings resulting from new therapies. For example, the health care savings reaped from the development of vaccines that prevent such illnesses as influenza, polio, hepatitis and meningitis have virtually paid for the entire investment in NIH research.

Finally, the international implications of allowing clinical research to falter are enormous. We are beginning to see signs that other nations are picking up the clinical research banner that America is dropping. A January 1992 editorial in Science magazine noted that the United States would remain a substantial factor in biotechnology but that a dominant role is being frittered away.

Having described the implications of the clinical research crisis, I will now describe the problems creating it. Again, these are going to be a bit repetitious. We will keep them brief. Unfortunately, the challenges to clinical research are on many fronts and require multipronged solutions. First is the issue of personal debt. American physicians are opting out of research careers for a variety of reasons, the most obvious of which is medical school tuition debt. A low-paying research fellowship is not an option for many indebted medical school graduates.

The second problem only exacerbates the first, the loss of established investigators. Young physicians see their mentor struggling or see them abandon their research careers because of inadequate funding and they say, "Not for me." The AMA reports that between 1985 and 1993 the number of physicians reporting research as a major professional activity fell by 23,268 to 14,716, this occurring while the total number of physicians grew dramatically.

Third, there are fewer academic physicians. Even those interested in and trained for a job in academic medicine cannot find one as the faculties rapidly contract under the pressures of changing

health care economics. This may even result in some medical schools closing altogether.

This brings me to the fourth problem, NIH peer review. This issue was first raised in the Institute of Medicine report, but in addition, as has been noted, a special outside committee of the division of research grants chaired, I believe, by Dr. Williams at NIH also concluded that some clinical research proposals are inadequately reviewed by study sections that see only a minimal number of research grants.

Senator Hatfield, we have discussed this problem with the council of AFCR and there is a strong belief that the chance of securing NIH funding is much greater with basic science studies than clinical proposals. In an informal discussion of this topic, we learned that many of us were having the same experience. About 5 or more years ago grants that proposed to pursue the clinical relevance of the basic science discovery had a reasonable chance of being NIH funded. Today, however, NIH peer reviewers give the highest marks to research focused on the narrowest cellular and subcellular scientific questions, not the broader physiologic implications of such science.

Grants that look at the systems physiology or the clinical relevance of molecular biology are often described as unfocused, descriptive or phenomenal logic, and are frequently doomed to fall below the NIH pay line.

The fifth problem confronting clinical research is the financial pressure on the academic medical centers. As outlined by Dr. Kohler, competition in the healthcare marketplace is having an adverse effect on clinical research. Some 5 years ago, you could walk into most any patient ward in a teaching hospital and find research patients mixed in with those receiving noninvestigational treatments. Today's wards are understaffed and dealing with constrained resources. Complicated clinical research protocols are not easily completed in this setting.

Researchers and their patients seek a safe haven from healthcare competition in the general clinical research centers, the GCRC's, which are underfunded for the task. In fact, to our distress, the fiscal year 1997 President's request for the GCRC's would hold them to a subinflationary increase of less than 1 percent, effectively a programmatic cut.

Some of the solutions to the problems are included in S. 1534, the clinical research enhancement bill you have introduced. Your bill is not radical. It simply mandates the initiatives recommended by the Institute of Medicine. As we have reviewed the cost of your bill, it would appear to be relatively small. The total annual cost of what you have proposed is $36 million, a mere 0.3 percent of the current NIH budget. Clearly the amount of money involved is not excessive in the opinion of the 80 organizations that support the legislation as part of their advocacy effort on behalf of the NIH.

Of course, the NIH's ability to pursue the initiatives you proposed would be substantially enhanced were the Congress to implement another Hatfield initiative that AFCR strongly supports, the creation of the medical research funds to supplement the NIH budget. With the downward pressure on Federal discretionary

spending, such a fund may be critical to maintaining America's No. 1 status in medical science.

In closing, Senator Hatfield, let me thank you on behalf of physician scientists and their patients for bringing your considerable clout to the crisis confronting clinical research. In addition, let me convey the appreciation of the AFCR and all medical scientists for your longstanding efforts to increase the NIH budget. You have been the general in our battle for a strong and vibrant National Institutes of Health.

PREPARED STATEMENT

To extend this military analogy, I have heard your comparison of the biomedical research crisis to a time in the 1960's when the Pentagon's advocates reminded us that the Russians are coming. As you have noted, today it is the viruses that are coming and I hope you can convince your colleagues that they are far more threatening to the American people than the Russians turned out to be. Thank you.

Senator HATFIELD. Thank you for your political commentary as well as your medical one. [Laughter.]

[The statement follows:]

PREPARED STATEMENT OF DR. MONICA M. FARLEY, ASSOCIATE PROFESSOR OF MEDICINE, EMORY UNIVERSITY SCHOOL OF MEDICINE, CO-CHAIR, PUBLIC POLICY COMMITTEE, AMERICAN FEDERATION FOR CLINICAL RESEARCH

Good afternoon, Senator Hatfield, and thank you for giving the American Federation for Clinical Research (AFCR) the honor of participating in this hearing. The AFCR has followed with great interest and enthusiasm your efforts to bring attention to the crisis that confronts our nation's clinical research effort culminating in the introduction in January of S. 1534—the Clinical Research Enhancement Act.

The problems confronting clinical researchers and their patients have received much attention but little action over recent decades:

—In 1979, former National Institutes of Health (NIH) Director James Wyngaarden gave his seminal presentation characterizing "the clinical investigator as an endangered species."

—In 1992, Rockefeller University Professor Edward Ahrens published a book entitled The Crisis in Clinical Research: Overcoming Institutional Obstacles further detailing many of the problems identified by the Institutes of Medicine (IOM).

—In March of 1994, the Annals of Internal Medicine published an article by Yale Professor Edwin Cadman—"The Academic Physician-Investigator: A Crisis Not to be Ignored."

—In September of 1994, the IOM published a report on the opportunities and challenges confronting clinical research.

—Late last year, the journal Nature Medicine published a report documenting a slowing of medical discovery in the United States over the last several decades.

—More recently, even the lay press has begun to report on attrition from the ranks of the physician scientist.

—Finally, Dr. Varmus has appointed a panel on clinical research, and the AFCR anxiously awaits this panel's recommendations and implementation.

In summary, it seems to the AFCR that the problems confronting clinical research have been studied and analyzed sufficiently. It is time for action—and that is why the AFCR is so enthusiastic about your legislation.

IMPLICATIONS FOR THE COUNTRY

Why is it so important to address the problems confronting clinical research? What is the impact of a weakened clinical research effort?

—First, improvements in patient care and the prevention of disease depend on clinical research, which brings basic scientific discoveries to the benefit of human beings. When clinical research is slowed, so is progress in medicine. Patients out there waiting for "the cure" must wait longer.

—Second, the fruits of clinical research are often taken by industry and developed into new drugs, vaccines, or other health care products. These new products boost our economy and create jobs.

—Third, while not all medical discoveries reduce health care costs, many do, as documented in NIH reports on the cost-savings resulting from new therapies. Certainly, it is less expensive to vaccinate against polio and hepatitis than it is to treat these diseases. It is less expensive to eradicate the H. pylori infection that causes peptic ulcer disease in two weeks than to treat the disease for decades.

—Finally, the international implications of allowing clinical research to falter are enormous. We are beginning to see signs that other nations are picking up the clinical research banner that America is dropping. A February, 1992 article in Fortune Magazine reported "pharmaceuticals and biotech" to be one of the few industrial areas in which the United States maintained international dominance. However, the article cautioned that European companies were expected to grow rapidly and that the Japanese share of new drug patents had doubled over the previous fifteen years. This concern was echoed in a January, 1992 editorial in Science Magazine, which noted that the U.S. would remain "a substantial factor" in biotechnology but that "a dominant role is being frittered away."

THE PROBLEMS

Having described the implications of the clinical research crisis, I will now describe the problems creating it. I wish I could tell you that one or two discreet and unrelated factors are involved. Unfortunately, the challenges to clinical research are on many fronts and require multi-pronged solutions.

First is the issue of personal debt. American physicians are opting out of research careers for a variety of reasons, the most obvious of which is medical school tuition debt. A low-paying research fellowship is not an option for the indebted medical school graduate. The average debt of the 1981 medical school graduate was $20,000. By the mid-1990s, that amount has tripled to $63,000. A research fellowship paying $28,000 to $30,000 is a financial impossibility for some individuals with accumulated debt.

The second problem only exacerbates the first: the loss of established investigators. Young physicians see their mentors struggling or see them abandon their research careers because of inadequate funding, and they say, "not for me!" The AMA reports that between 1985 and 1993, the number of physicians reporting research as a major professional activity fell from 23,268 to 14,716—this occurring while the total number of physicians grew dramatically.

Third, there are fewer academic positions. Even those interested in and trained for a job in academic medicine often cannot find one as faculties rapidly contract under the pressures of changing health care economics. This may result in some medical schools closing all together.

We see evidence of decreasing physician investigators in the NIH extramural grant program as well. In 1970, physicians made up 43 percent of all principal investigators on funded grants. By 1987, this had dropped to 30 percent. Applications for NIH grants have grown dramatically in the past fifteen years, but most of the growth has been among Ph.D.'s. As the overall success rate for funding approved NIH grants has dropped, the result is an inevitable further squeeze on the physician investigator.

This brings me to the fourth problem: NIH peer review. This issue was first raised in the IOM report. But, a special outside committee of the Division of Research Grants also concluded that some clinical research proposals are inadequately reviewed by study sections that see only a minimal number of clinical research grants.

Senator Hatfield, we have discussed this problem within the Council of the AFCR, and there is a strong belief that the chance of securing NIH funding is much greater with basic science studies than clinical proposals. In an informal discussion of this topic, we learned that many of us were having the same experience. Five or more years ago, grants that proposed to pursue the clinical relevance of a basic science discovery had a chance of being NIH funded. Today, NIH peer reviewers give the highest marks to research focussed on the narrowest cellular and sub-cellular scientific questions, not the broader physiologic implications of such science. Grants that look at systems physiology or the clinical relevance of molecular biology are described as "unfocussed," "descriptive," or "phenomenologic" and are frequently doomed to fall below the NIH payline. Thus, instead of taking advantage of the physician's ability to take basic science information from the laboratory to the patient's bedside, or from the patient back to the lab, the NIH peer review system encourages

physicians to confine themselves to the same scientific questions and projects being pursued by Ph.D.'s.

The fifth problem confronting clinical research is the financial pressure on the academic medical centers. Finally, competition in the health care marketplace has affected clinical research in three more important ways:

First, there is an increasing institutional demand for the clinical services of physician faculty. The Institute of Medicine report noted:

> The economic necessity of maintaining a clinical department in financial balance has placed a greater emphasis on the clinical care component of a department's activities * * *. Although junior faculty members are recruited with the expectation that they will develop creative lines of investigation, the pressures of starting an academic practice, building a referral base, and contributing to departmental coffers can be overwhelming.

The professional activities of faculty members in clinical departments are tied to the financial stability of academic medical centers, which have come to depend on clinical service income. In 1970, professional service income represented approximately 12 percent of total revenues to U.S. medical schools. By 1990, this had grown to approximately 40 percent and has continued to expand during the first half of this decade. To survive, academic institutions require clinical faculty to see patients, see patients, and see patients—thereby reducing time available for research and for the pursuit of grant support.

The second problem within the academic institutions is the loss of available internal funding to subsidize clinical research. In the past, the "profit margin," if you will, of clinical service revenue was used for the support of research career development, as bridge support for young investigators who had been unable to secure outside support, as bridge support for established investigators who temporarily lost their outside funding, and as support for the clinical research infrastructure. The AAMC has estimated such funding to have been at a level of $800 million, but those days are over. Most institutions are losing their "rainy day fund" for clinical research, and in fact, many academic medical centers are in major financial difficulties.

The squeeze of increasing competition in the health care marketplace has had a major impact on clinical research. In fact, in a study conducted for the Department of Health and Human Services, Lewin/VHI noted that "financial pressures brought about by managed care may reduce cross-subsidies historically used to support * * * clinical research activities." Many are concerned that research is one of the "costs" being squeezed out of the health care system by the growth of managed care. A recent article in Time Magazine referred to managed care as "the new medicine [which] by its nature abhors complexity and innovation." The article stated that managed care companies are "bound by law and competition to avoid * * * research." Unfortunately, not only will insurance companies not pay for experimental therapies but now they often will not even pay for the usual care when the person is part of a research study. This situation provides clear rationale for the proposal you and Senator Harkin initiated to set-aside a percentage of insurance premiums for a medical research fund to be administered by NIH.

Academic institutions are now confronted with the need to compete in the health care marketplace more than ever before or passing the costs of doing research on to consumers as was done in the past. The latter is no longer an option. The presence of research—like the presence of students and residents—makes the cost of providing care higher for teaching institutions. They simply can not compete with non-research institutions if they pass the indirect and infrastructural costs of research onto third-party payers.

Five years ago, you could walk into most any patient ward in a teaching hospital and find research patients mixed in with those receiving non-investigational treatment. Today's wards are staffed by fewer nurses. Complicated clinical research protocols are not easily completed in this kind of setting. Researchers and their patients seek a safe haven from health care competition in the General Clinical Research Centers (GCRC), which are underfunded for the task. In fact, to our distress the fiscal year 1997 President's request for the GCRCs would hold them to a subinflationary increase of less than 1 percent—effectively, a programmatic cut.

## THE SOLUTIONS

Some of the solutions to the problems are included in S. 1534, the Clinical Research Enhancement bill you have introduced. Your bill is not radical—it simply mandates the initiatives recommended by the IOM. As recommended by IOM, your bill would:

—address the physician indebtedness problem by expanding the existing NIH loan repayment program to the extramural community;
—help young investigators get established through the creation of 5-year career development awards for clinical researchers;
—assist established investigators pursuing limited "pure" clinical research studies through the establishment of small "innovative medical science awards;" and
—address the peer review problem by creating a separate review group for the two new awards and mandating implementation of changes in peer review as recommended by the DRG's special committee.

Of course, all of this require resources. However, as we have reviewed the cost of your bill, it would appear to be relatively small. Fully implemented, the expansion of the loan program would cost approximately $1 million per year. The career development and small grants program would cost approximately $35 million per year. To our knowledge, nothing else in the bill would entail significant expenditures by NIH. Thus, the total annual cost of what you have proposed is a relatively small $36 million—a mere 0.3 percent of the current NIH budget. Clearly, the amount of money involved is not excessive in the opinion of the 80 organizations that support the legislation as part of their advocacy effort on behalf of the NIH.

Of course, the NIH's ability to pursue the initiatives that you propose would be substantially enhanced were the Congress to implement another Hatfield initiative that AFCR strongly supports: the creation of a medical research fund to supplement the NIH budget. Clearly, with the downward pressure on Federal discretionary spending, such a fund must be created if we are to keep American number one in medical science.

Senator Hatfield, let me close by thanking you on behalf of physician scientists and their patients for bringing your considerable clout to the crisis confronting clinical research. In addition, let me convey the appreciation of the AFCR and all physician-scientists for your long-standing efforts to increase the NIH budget. You have been the general in our battle for a strong and vibrant National Institutes of Health. To extend this military analogy, I have heard your comparison of the biomedical research crisis to a time in the 1960's, when the Pentagon's advocates reminded us that the "Russians are coming." As you have noted, today it is the viruses that are coming, and I hope you can convince your colleagues that they are far more threatening to the American people than the Russians turned out to be.

**STATEMENT OF DR. GORDON WILLIAMS, DIRECTOR OF ENDOCRINE-HYPERTENSION, BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MA**

Senator HATFIELD. Dr. Williams.

Dr. WILLIAMS. Senator, I think I will probably take Dr. Kohler's approach. The last person on the panel, everything has been said that needs to be said and either I can say amen and we can go on to something else or I can modify some of my comments, and I think I will just take a chance to modify some of them.

The committee, the clinical research study group that has been discussed extensively here, was a committee that was formed by the division research grants and I think it is important to point out parenthetically that the committee was formed by NIH, not by some outside group, to look at a problem that the people at NIH certainly heard much about; that is, the decreased support for clinical research and the NIH approach to how they fund was part of the problem.

I think that is a very important point that we have to make in relationship that this was actually formed by NIH. The committee met many times over in 1994 and came up with a report that was presented at the DRG advisory committee in November 1994. Perhaps it is important to point out in background that study sections are the vehicles in which the reviews are taking place of the applications that go to NIH for external funding, and that except for some epidemiologic applications, there is no specific study section that reviews clinical research applications. As Dr. Varmus pointed

out, that resulted in a series of problems that the committee addressed.

There are about 20,000 applications that are reviewed by NIH each year, and our analysis of these applications—we looked about two-thirds of the applicant load—was first to determine was there a difference in the success rate of patient-oriented versus laboratory-oriented research applications and then does it have anything to do with the study compositions, study section composition.

I think it was clear from three perspectives, that has been stated by many individuals, that the funding success rate was less if you had a patient-oriented research and highly significantly less in terms of funding patient-oriented research versus laboratory-oriented research and this was, therefore, the perception of a large number of people that we received oral testimony from, was confirmed by this objective data. Some of the, quote, "anger" that you talked about was reinforced by this, but again, I think it is important to emphasize that NIH was the one who developed this panel to begin with.

As Dr. Varmus pointed out, one of the major problems was the shift in the composition of the clinical study—of the study sections. Dr. Loriaux pointed out the fact that there is this fluid nature of the composition of the study sections. They usually serve for 4 years and their expertise reflects the expertise of the grants that were just reviewed by that study section, so as the grants shifted to a more basic orientation, the number of the people who were selected by to replace the ones on the committee, also had to shift to reflect that particular expertise. And so it wasn't a concerted effort on the part of NIH to get rid of clinical research; it was simply the evolutionary process of how the reviews take place.

And that led to the finding that if you happen to be—and your grant was reviewed, application was reviewed in the study section in which the load of clinical research applications was less than 30 percent, you had only a 60-percent chance of being in the top 20 percent grants as opposed if you had a laboratory-oriented research grant, so a decided disadvantage if you were in that particular type of study section.

So certainly study section composition is a real problem. Now how could one correct these? We thought of at least three steps for this part of our report. The first one was that we may—we have to ensure that the grants that are patient-oriented grants are reviewed by study sections in which the majority of the grant applications are patient-oriented research grants. Now this may mean starting some new study sections that are patient-oriented study sections. The problem, because remember the process that I talked about, could, over a period of as short a time as 8 years with the cancer study section, evolve a clinical research study sections into a basic research study section, so that may or may not solve the problem that we talked about.

The second thing is more patient-oriented application reviewers need to be recruited would seem to be a fairly straightforward process. There are now about 550 individuals who have been identified that would be willing to serve on these types of study sections.

And perhaps most importantly is a clearly defined criterion need to be developed for high quality patient-oriented research that can

serve as guidelines for review bodies. It is likely that some of these criteria will be different from those used to evaluate laboratory-oriented research applications.

I think it is clear to emphasize the fact that making these changes is not going to correct the entire crisis in clinical research. There are multiple problems. We need to change, perhaps, our medical school structure. We need to have more adequate private and, as pointed out, public funding to meet all of our clinical investigative needs but we think that a major symbolic and perhaps a substantial financial signal will be given by appropriate implementations of the steps outlined by this study group.

In summary, the present analysis which was developed to determine whether the patient-oriented research applications fared less well in the current NIH review process clearly indicates that is correct. These analysis also provide entree to suggest modifications of the system to improve the fairness of the review process as one way of addressing the overall problem of declining interest in expertise in patient-oriented research.

To date, the recommendations of the clinical research study group have been difficult to implement even though they were accepted by the DRG advisory council in May. I think it is clear to say part of that are for the reasons that Dr. Varmus pointed out, not the least of which is there is no current director of the DRG, so it is difficult to implement procedure if you do not have a boss in place that can actually carry through on that and rightly so. Dr. Varmus points out that is one of the major things that he is doing now at present time.

One positive step obviously has been the submission of the bill under discussion today which, among its provisions, specifically directs NIH to implement the recommendations of the clinical research study group. Therefore, there are a number of problems that beset the current DRG study section review procedures. The few steps outlined by that committee's report seemed mandatory to restore the integrity of the funding process and require little, if any, increase in funding.

If, as previously stated by Dr. Varmus, that biomedical research funding has reached a steady-state position, a condition which I personally hope is not true for all of our sakes as we pointed out before, then it is imperative that the various components of the biomedical research committee are treated equally. Without implementation of this crucial safety net that I have outlined, the patient-oriented research component of this community may be critically damaged.

I think the other thing that I would like to add that we have not discussed today is the critical and maybe linchpin role of the clinical research career enhancement report, which is part of the bill. One of the major problems, we have talked about how to maintain the individuals who are seeking careers in clinical investigation in that given all of the pressures that Dr. Loriaux described on their times and efforts and giving them 5 years of funding at a critical point when they are at a junior status of their careers is probably an incredibly important aspect of maintaining and enlarging this crew of individuals who are going to be the clinical investigators of the future.

PREPARED STATEMENT

I think in closing I probably ought to also point out, I am an eternal optimist. So therefore, while I think we are in a crisis state, I think it is clear that the pathway that needs to be followed is outlined in your bill, is one that will accomplish many of the purposes that we all desire in terms of clinical research. I do not think anyone, whether they are someone who studies genes or someone who studies drugs or devices, will argue with the rightness, if one wants to use that term, of the—are the critical, central point of clinical investigation and that we need to support that particular part of the community much better than we have in the past.

Thank you for allowing me to share my thoughts with you.

[The statement follows:]

PREPARED STATEMENT OF DR. GORDON H. WILLIAMS, CHIEF, ENDOCRINE-HYPERTENSION DIVISION, BRIGHAM AND WOMEN'S HOSPITAL, PORTLAND, OR

I appreciate the opportunity to testify before you on the problems affecting clinical research and potential solutions to those problems. I am here to describe to you the findings of the National Institutes of Health (NIH) Division of Research Grants (DRG) Clinical Research Study Group.

Considerable concern has been raised recently in a number of quarters over the health of our national clinical research program. Evidence of erosion of this program has been observed at many levels, as discussed by others today. Among the causes cited for this is the perception of a decreased support for clinical research by the NIH. To address this perception, the DRG (the body that handles the review of investigator-initiated grant applications) formed the Clinical Research Study Group in February 1994. This group met several times that year, receiving public testimony from many experts from the clinical research community and objectively evaluating the fate of clinical research grant applications submitted to NIH for funding. A report of our group's finding was presented to the DRG Advisory Council in November 1994.

Study sections are the vehicles used to evaluate these applications. Except for Study Sections which review epidemiologic applications, none are specifically designed to review patient-oriented research grant applications. Thus, most of the patient-oriented applications are reviewed in Study Sections in which these applications comprise only a minority of the total reviewed by any given Study Section.

Study Sections review 20,000 research grant applications each year. We analyzed two-thirds of a year's application load. The analysis had two primary goals: First, to determine if there was a difference in the success rate of patient-oriented versus laboratory-oriented research grant applications; and second, to determine whether these differences are related to Study Section composition.

Three different approaches suggest that patient-oriented applications fare less well in the NIH review process than laboratory-oriented applications. Most disturbingly, the funding rates for patient-oriented were highly significantly less than for laboratory-oriented research applications. Thus, it is clear that patient-oriented research applications fare less well than laboratory-oriented research applications in the NIH review process, thereby confirming the perception expressed by those who gave oral testimony from our group.

Our analyses also suggest a potential reason for these differences: Study Section composition. The discrepancy between the rating of patient-oriented versus laboratory-oriented research applications was exaggerated in those Study Sections, which as a group had a patient-oriented research application load of less than 30 percent. Patient-oriented research applications reviewed by members of these Study Sections fared substantially worse than laboratory-oriented applications. For example, the probability that a patient-oriented grant application would be in the top 20th percentile was less than 60 percent of expected. In contrast to those Study Sections with a low patient-oriented application load, in those with a substantial load (greater than 50 percent), these applications had similar success rates as laboratory-oriented applications in general.

How would one correct this problem? At least three steps would be necessary. First, patient-oriented applications would have to be reviewed in Study Sections in which at least 50 percent of the applications are patient-oriented research applications. This may mean establishing new patient-oriented research Study Sections.

Second, more patient-oriented application reviewers need to be recruited. Third, a set of clearly defined criteria needs to be developed for high quality patient-oriented research that can serve as guidelines for review bodies. It is likely that criteria will be different than those used to evaluate laboratory-oriented research applications.

Will these changes correct the present crisis situation in clinical research? The answer is clearly "no", as the problems involved in meeting our clinical investigative needs are multi-factorial. Changes will need to be introduced in our medical schools and in more adequate private and public funding to meet our overall clinical investigative needs. However, a major symbolic, and a substantial financial signal will be given by appropriate implementation of these steps.

In summary, the present analysis was developed to determine whether patient-oriented research applications fare less well in the current NIH review process. These objective data provide strong support to the patient-oriented research community's contention that their investigator-initiated applications are not reviewed equitably at the NIH. These analyses also provide entree to suggested modifications of the system to improve the "fairness" of the review process, as one way of addressing the overall problem of declining interest and expertise in patient-oriented research. To date, even though the clinical research study group full report was excepted by the DRG Advisory Council in May 1995, there is little evidence that any of its recommendations have been implemented. One positive step has been the submission of the bill by Senator Hatfield entitled "The Clinical Research Enhancement Act of 1996" which, among its other provisions, specifically directs NIH to implement the recommendation of the Clinical Research Study Group.

Thus, although a number of problems beset the current DRG Study Section review procedure, the few steps outlined above are mandatory to restore the integrity of the research funding process and require little, if any, increase in funding. If, as previously stated by NIH Director Dr. Harold Varmus, biomedical research funding has reached a steady-state position (a condition I hope is not true), then it is imperative that the various components of the biomedical research community are treated equally. Without implementation of the crucial safety net outlined above, the patient-oriented research component of this community may be critically damaged.

Thank you for providing me the opportunity to share my thoughts with you.

## FIRST AWARDS

Senator HATFIELD. Thank you very much, Dr. Williams. I have to go back to start with Dr. Kohler and his testimony and refer to points that I would like to have you merely expand a little bit on.

Dr. Kohler, you have indicated the importance of increasing the numbers of first awards as critical to the future of research in this country. In your judgment, does the structure of the first awards need to be changed in order to benefit clinical researchers?

Dr. KOHLER. I think the main thing that needs to occur is that there be adequate numbers of rewards in place for people who are interested in this type of career, and frankly, I am not sure that it needs to be changed very dramatically but they just need to be available. They are available, but the problem sometimes is after the first is their life and that falling-off-a-cliff phenomenon after that first award perhaps is the transition that needs some attention in terms of a career pathway that young investigators would want to pursue.

Senator HATFIELD. Of course, you link that back to the academic health centers, and referring back to the IOM panel recommendations, that these institutions review their promotion guidelines to give further recognition to the scholarly contribution made by clinical researchers and that there be a system of reward mechanism established as well.

To your knowledge, has the academic health centers addressed this issue and what specifically have you done at Oregon Health Sciences University?

Dr. KOHLER. Well, we have made sincere efforts to utilize clinical research and reward research appropriately. I will say that we probably have not done enough in this particular transition state because we, like many academic health centers in this country, are forced to look at funded research as a criterion as opposed to unfunded research, which may be very laudable but not necessarily in the same category when people come up for review for promotion or tenure considerations.

So I think it is creating some kind of continuation of effort that can be funded that most academic health centers are going to look at as important for the future of people such as clinical investigators.

Senator HATFIELD. When?

Dr. KOHLER. When will that occur? Well, I think some of the things that have been discussed here today I think create opportunities for that to happen. I do believe—I actually used to chair a study section myself and I saw the phenomenon that Gordon described occurring as we began to look more and more at basic research grants and less at clinical grants, and I do remember Dr. Farley's comments coming back now in terms of reviews of clinical grants.

I have to say it is much more difficult to study people and get meaningful data from people than it is to study tissue culture cells, many molecular techniques or even laboratory animals. It is quite a feat to keep a group of people who have a choice together and study protocols to come out with unambiguous answers, so I think that is part of the thing also.

In terms of just the efficiency of a research protocol, it is a whole lot easier to do with cell culture or molecular techniques with groups of patients that need to be held together for a period of time. So we perhaps have not done as much. We have tried to foster research and make it an attractive career path, but I think we have not done as much nor have any other people that I know of in academic health centers in terms of the promotion-tenure question.

Senator HATFIELD. Leading from that point into your comments, Dr. Loriaux, you mentioned—I believe you called the clinical investigators a financial liability.

Would you explain further as to what it is about them that creates this financial liability and how can it be reversed?

Dr. LORIAUX. Well, the reason I believe they are a liability is that if they attain success, they still are unable to obtain funding. So if you have a successful clinician, that clinician can make all of his or her salary and make all the ancillary contributions to school and teaching, research and patient care, research in a way of providing a substrate that you can ask. Basic scientists in this setting can supply the lion's share, if they are successful, of their salary, and my belief is it will always have to subsidize somewhere around 20 percent of the laboratory scientists.

Senator HATFIELD. You are speaking of the financial benefits accruing from the research?

Dr. LORIAUX. From the research. In other words, their financial benefits will be success in the grants market which will supply the

lion's share of their salary and so you have all the benefits of this active and productive research for a very small cost.

The clinical investigator cannot see enough patients to make any significant amount of his or her salary if they are activity being a clinical investigator, nor are they going to be able in the current climate to be very successful in the grants market. So no matter how good they are and how well they succeed, you are always at risk of having to subsidize them from funds right now that we do not really have, and when you have somebody who is really successful, you want them to continue their career and continue to support them. Everybody's a little shy about that right now because in today's time of austerity, the funds just are not there to ensure that they are going to be able to be carried through and that is the reason why to the best of my view.

Senator HATFIELD. You are the director of the general clinical research program here?

Dr. LORIAUX. Right.

Senator HATFIELD. What resource does that program provide Oregon Health Sciences University that would not otherwise be available for clinical researchers, and would expanding the clinical research center program be helpful or what would you add to that?

Dr. LORIAUX. Well, the clinical research center is a wonderful resource and what these are, there are 72, 73 of those now scattered around the country. They are actually declining in number. I can remember when there were 85. Probably they represent somewhere around 600 research beds. Clinical center had 450, still does have 450. It is somewhat reduced down in number now, so I do not know how many active beds but at one time the clinical center represented more clinical research beds in a single place than all of the rest of the United States. It is probably a little more equalized now.

What this represents is a laboratory for the clinical investigator in which the clinical investigator can work. There are patient rooms in there which have all the amenities of a hospital room as a rule and there are places you can administer materials to a patient. You can withdraw blood. You can direct various kinds of samples, urine, saliva, whatever you need to have. There is a cadre of nurses there and they are usually rather generous in terms of nurse-to-patient ratio. They generally have a kitchen so that you can supply specialized diets for controlled settings. You begin to control all the variables of the experiment. They have a place, a method for accessing blood samples, storing them, preparing them and generally there is a core laboratory associated with it so that of the basic studies and then many—and in some cases the more sophisticated studies necessary for the research unique to that clinical research center can be done on site.

And all this is paid for through the grant, so that if I find an interesting patient and I have an approved study through the institutional review board, in other words, the ethics of this thing and the costs and benefits have all been assessed and it is viewed to be ethical to do this study, I can use this resource to admit the patients for study and now so long I can make a salary along with it, then I can be there to do the work.

I mean, the laboratory is there and the laboratory is funded. We are fortunate because we have a big part of the puzzle here. There is a way to sustain the investigator to use the laboratory. That is the issue.

Senator HATFIELD. Is there any way to evaluate the capacity, unused capacity or excess capacity, that exists today scattered throughout this country in the research centers, clinical research centers?

Dr. LORIAUX. Well, there are ways you can begin to approximate it. The reason we will never really know is because it will be limited by two things, first, the number of beds and associated with that is the number of outpatient visit space that you can have and the nursing power associated with it.

There is another thing called scatter beds. You do not have to build everything into a clinical research center. For example, we want to work on trauma. We want to work on the devastating arrhythmias of the heart. We can do those in the coronary care unit. We can do those in the surgical intensive care unit. These are called scatter beds and we can support that with nursing staff and money.

Senator HATFIELD. You are saying we can maximize the existing facility to a greater degree if we had a strategy?

Dr. LORIAUX. What I am saying is there is a lot of—yes. There is a lot of unused potential there and, you know, many of the investigators who should be using CRC's do not use them because they have actually not been encouraged to use them or do not know the power of the tools that we have, and right now it is somewhat limited by dollars, could we expend the dollars, increase the number of dollars, even for the laboratory research. But what we are talking about are, you know, increase in the amount of research that has been ongoing, and so I think there is a huge amount of unused potential.

Research is going on in clinical investigation now or is in places where there is a lot of money that flows in, so some of the most exciting research is happening in orthopedics, for example, some of it in dermatology. Some of the most exciting research is happening in trauma and these are places where they make enough money off the medical enterprise that they can use that to subsidize the research initiative.

If you go back to my discipline, for example, endocrinology, you do not make any money and there is not a dollar left over to put back into research. That must come from some other place and that is true for most of the cognitive disciplines like infection, diseases, rheumatology, and so on and so forth.

Senator HATFIELD. Dr. Farley, you speak about the bias of patient-oriented research and the proposals in the NIH reviews and studies. Assuming that the recommendations that will emerge out of the Nathan group, do you feel that there will be sufficient resolution of this issue outside of establishing special award programs for clinical investigators or do you think that is in addition to?

Dr. FARLEY. Well, I think the issue is complex and among our membership, as we have discussed in our national council, there is a sense that the peer review system has been there. It is a time honored system and that it more or less works. The problem is, I

mean, there are problems and they include the content of your grant maybe not matching the makeup of the study section. They also very importantly include the pay line and the pay line is so low at this point even for basic science grants that the problem will remain even if we totally shifted it around and had a study section made up of only clinical investigators. The pay line of 12 percent is a daunting one.

So I do not think it is a single action that is going to solve the problems. I think the clinical investigators particularly affected by the low-pay line, the amount of money available, in that it takes, even for very well-established full-time scientists in this current area is taking multiple submissions before getting funding and a clinical investigator may have fewer resources to wait it out, to keep resubmitting. As they are resubmitting, they are taking on additional clinical work and essentially not managing to compete further for the funding in the future so that they cannot wait one or two further submissions and successfully maintain their research career.

So a single change is not going to fix the whole problem, but we are encouraged very much by the idea of trying to enhance the representation on the current study section system, and among our council members, that was considered preferable to pulling clinical research completely out and establishing a completely separate clinical research study section for all clinical research issues coming through.

Senator HATFIELD. Asking the same question I propounded to Dr. Kohler, are you aware of the academic health centers who have seriously and with results addressed the matter of promotion guidelines and reward mechanisms relating to clinical researchers to demonstrate their scholarly contributions? And if not, what is going to have to happen in order to stimulate a national movement amongst the academic health centers?

Dr. FARLEY. Well, I think it is the worst possible time for an academic health center to expand whom they give tenure to. I mean, these are incredibly difficult economic times in academic medical centers all across the country. I am in a department of medicine discipline and departments of medicine across this country are under—I mean, chairmen are dealing with dollars and cents more than patient care issues right now and it is a time where, when people are at a stage that their grant is out and they are in a resubmission process, in the past the department of medicine chairman might have had a fund of money that could be used to supplement them and carry them over until their next submission. That money is not there.

If that is what you are referring to with rewards, I think that how we define promotion processes is perhaps a little different in that the concept of money to back up tenure anymore is kind of fading. There is not as much guaranteed, that tenure really means that you have guaranteed salary for life particularly not in clinical medicine.

But I am very discouraged by the fact that there is a sense that the pot of money from the clinical endeavor that could have in the past been used for research endeavors is not there, and those are, I think, where the past the first award, the person is their life past

the first award, that is where the problems are now sometimes beginning is that they get their first award but that at the next phase of the game they cannot immediately be competitive for an RO–1 grant and there is no money to keep them.

Senator HATFIELD. Well, I would like to submit a couple more questions to each of you to reply in writing, if you do not mind. They will be brief, but I notice the time keeps slipping by and we have another panel to be heard. So I will refrain from asking additional questions to the first three, but Dr. Williams, some have suggested that a separate study section, or sections, should be established in reviewing clinical research proposals. What is your view on this?

Dr. WILLIAMS. Well, the committee that I was on debated that question extensively and I think we were swayed with that may not solve the problem and the reason is the example of a clinical—of a clinical research study section devoted to cancer research that in the space of about 8 years metamorphosed to a basic science study section by the nature of the process that we talked about, so I think establishing separate clinical research study sections in and of itself, if you leave everything else the same in the system, it is probably not going to, in the long run, resolve the difficulties.

We have to be more aware of the nature of the fluid—the fluid nature of the study section composition and deal with that up front rather than assuming that, oh, we will fix the whole thing by putting them all in clinical science study sections because our committee's conclusion was that would not necessarily resolve the problem.

Senator HATFIELD. I believe also in the committee discussions that you came to a conclusion that the sections in their reviewing of these research proposals should have at least 50 percent——

Dr. WILLIAMS. Correct.

Senator HATFIELD [continuing]. Of the applicants they review involved in patient-oriented research. What was the threshold criteria arriving at that threshold?

Dr. WILLIAMS. Well, we divided the study sections up into 3 groups; that is, those who had more than 50 percent clinical research applications, those who had less than 30 percent and then the ones in between the two and roughly it divided the total number of patient-oriented research grant applications into thirds and then what we looked at is the success compared to what you would expect, and our criteria for success was that they were in the 20th percentile or lower value. That is a good grant.

And with that, there is no difference between the laboratory-oriented research grant success rate and the patient-oriented research grant success rate if the patient-oriented research grant was in a study section that reviewed at least 50 percent. If they were less than 30, then, as I said, it dropped down to 60 percent so it was a decided disadvantage. In between it kind of depended, as you might anticipate, on the other aspects related to a particular study section so that is how we arrived at the threshold of 50 percent.

Now if you think about the number of patient-oriented research applications submitted to NIH each year and you are going to put them in at least 50 percent, I am not going to create very many clinical research study sections unfortunately right now.

So by de facto, we may end up creating clinical research study sections just because of the volume that will be necessary to accomplish that, but if one just defined it as a clinical research study section without looking at the dynamic that could change it, I think we will have similar problems in the future.

Senator HATFIELD. Did you find that there was a sufficient number of clinical researchers willing to serve on these sections?

Dr. WILLIAMS. Yes; after the committee met, we then surveyed the clinical research community. This was headed by Pete Ahrens, who wrote the book on crisis in clinical research several years ago, and we came up with the 550 individuals who said that they would be willing to serve—who were patient-oriented investigators themselves who would be willing to serve on NIH study sections, which would be more than enough to meet the needs.

Part of the problem may also—this, again, gets into dynamics of a study section. Ideally you would like to have someone on for 4 years, come to all three meetings each year, to do that, and that might be more difficult for someone who is a clinical investigator for the reasons Dr. Loriaux pointed out than for someone who's a bench scientist to do.

So there may need again to be flexibility in how those study sections are composed, as well as we think, very important, there have to be a separate set of criteria that are developed to make sure that we are evaluating patient-oriented research applications the way we should be reviewing them rather than assuming, well, they are just like bench research applications. We should use exactly the same criteria.

Senator HATFIELD. And linked to that, you addressed the question of the writing of grants in relation to increasing those initial scores.

Dr. WILLIAMS. Right. That is one of the things that had been proposed a couple of years ago when this furor was in its infancy as well. Maybe clinical scientists aren't very good writers or maybe they do not know how to write to please a study section, which that second part may be true, because it then depends on what the study section is.

And the basis for that is if you look at the success rate of those that are resubmitted, they are considerably higher than the initial ones. Well, we looked at that and it turned out that is correct but it is correct for laboratory-oriented research grants as well as patient-oriented research grants and even the resubmitted ones are not funded as high for laboratory-oriented research as clinically oriented research grants.

So the problem exists. There is some education in probably trying to figure out what the study section really wants, but it still ends up being a disadvantage for the patient-oriented research application.

### STATEMENT OF DR. LYNN STEVENSON, CHAIR, OREGON BIOTECHNOLOGY ASSOCIATION AND DIRECTOR OF TECHNOLOGY TRANSFER AT THE UNIVERSITY OF OREGON

Senator HATFIELD. The third panel will consist of Dr. Lynn Stevenson, chairman of the Oregon Biotechnology Association, director of Technology Transfer at the University of Oregon; and Mr. Richard Sass, founder of PI Medical.

Dr. Stevenson, Mr. Sass, you have heard the general instructions about your full statement being placed in the record and you may proceed as you wish in summarizing or highlighting it, and then I will have a few questions.

Dr. STEVENSON. Thank you, Senator Hatfield. I really appreciate the opportunity to discuss biotechnology in Oregon today. I think that Oregon still has many obstacles to overcome on the way to developing a self-sustaining, competitive industry comparable to other States in the Western region of the United States. And this depends on the successful start-up and growth of companies based on technology from excellent research institutions.

As chair of the Oregon Biotechnology Association, president and CEO of a biomedical company and director of technology transfer at the University of Oregon, I would like to address the needs of start-up biotech companies in Oregon today. I have spent the last 16 years founding and managing biomedical companies and of these, four have gone on to become public companies. They have had operations in various States and I have been in Oregon for about 5 years.

There are about five key factors that are important for any biotechnology operation and these were outlined in the 1993 strategic plan for biotechnology in Oregon that was written in 1993. They include technology transfer, capital availability, human resources and education, shared facilities and a favorable regulatory environment. Due to time limitations, I would like to just address the first two factors today, technology transfer and capital availability.

Medical biotechnology takes novel ideas from the laboratory and develops products for patient use and I think that biotechnology companies have a very important role to play here in bridging the gap between medical institutions and basic science universities and larger companies which often do not make the efforts to go in and see what basic research is being developed in the universities.

My background is developing products out of medical research. I am currently CEO of Cascade Oncogenics and we are developing cancer diagnostic tests. Our first product is a test for breast cancer based on cyclin E. This protein was discovered at Fred Hutchinson Cancer Research Center and Rockefeller University, and research has been performed on it at the Dana Farber Center and Brigham and Women's Hospital.

Cyclin E has had a major role in the regulation of cell proliferation. In malignant cells the concentrations of this protein greatly increase and this provides a way to assess the severity of the cancer, to help in predicting outcome and selecting treatment. Our company is currently collaborating with local medical institutions to conduct clinical trials for this diagnostic test and this has happened fairly rapidly.

The time so far to bring this test to patients has only been about 4½ years since the discovery of the gene, and in contrast, the most widely used cancer marker test today, PSA, that is for the early detection of prostate cancer, took approximately 17 years from the time that it was described until its approval by the FDA. To speed up these times requires very close collaboration between biotech companies and the research institutions.

So what are the difficulties that we face, particularly in Oregon? One is to have a critical mass of medical and biological researchers in the State. The investigators that we have in Oregon are very good and have made a lot of basic discoveries that are important for commercialization, but there are not enough of them. The universities here need additional funding to recruit and retain excellent researchers, both the basic and the clinical, because we need both.

Oregon research institutions have realized the need for active technology transfer and all of them have responded to that need, even in a time of extremely limited resources. They have changed administrative policies. They have increased the professional technology transfer of personnel and what are the results? In Oregon, it is small compared with other States but there have been at least 10 companies formed during the last 4 years based on university technology and 8 of these have been biotech companies.

People in the industry are grateful for this support and we support the efforts of the universities to increase technology transfer. But without additional resources, they are at risk. With this increasing awareness on the part of the universities, I think we need additional research faculty to support and strengthen the research areas where Oregon institutions are already recognized leaders. I think in this State we have to build on our strengths. For example, molecular biology at the University of Oregon is ranked in the top 25 percent in the Nation and you have heard about some of the strengths at Oregon Health Sciences University.

No biomedical products can enter the marketplace without clinical research and being tested on patients. I think by building on our strengths, Oregon can most efficiently develop international recognition. Just as important from an industry point of view, wide recognition of research expertise attracts the larger biopharmaceutical companies and it also attracts investors.

That brings me to the secondary area of major need that I wanted to address today, that of capital access. There's a large gap in the availability of capital to fund the growth of biotechnology companies in Oregon. A recent study, partly sponsored by the Oregon Biotechnology Organization, has estimated this gap between $100 and $200 million.

Fortunately in Oregon we have the Oregon Resource and Technology Development Fund, ORTDF, which is one of the most successful seed investment funds in any State. This was established in 1986 by a far-sighted legislature, but since then its support has been reduced. ORTDF has invested in 10 biotechnology companies at the seed stage, most of which are using university technology. However, there is a real need for funding sources to provide follow-on capital as these companies grow. Biotechnologies require more capital before they get a product to market, especially therapeutic products, and without capital, they will fail.

PREPARED STATEMENT

One more point. Several Oregon companies depend for their research and development effort on winning small business innovation research grants. These are provided by most Federal funding agencies. These excellent awards are absolutely necessary for the

survival of biotechnology in Oregon today and we would urge their continuing support.

Senator HATFIELD. Thank you.

[The statement follows:]

PREPARED STATEMENT OF LYNNOR B. STEVENSON, PH.D., CHAIR, OREGON BIOTECHNOLOGY ASSOCIATION, PORTLAND OR

Thank you for the opportunity to discuss biotechnology in Oregon today. Oregon still has obstacles to overcome on the way to developing a self-sustaining competitive industry comparable to that of other states in the western region of the United States. This depends on the successful start-up and growth of companies based on technology from excellent research institutions. As Chair of the Oregon Biotechnology Association, President and CEO of a biomedical company, and Director of Technology Transfer at the University of Oregon, I would like to address the needs of start-up biotechnology companies in Oregon.

I have spent the last 16 years founding and managing biomedical companies. Of these, four have become public companies and two were acquired. The companies have had operations in seven states. Five key factors outlined in the 1993 "Strategic Plan for Biotechnology Development in Oregon" have been absolutely necessary for the success of these and other companies. These factors are technology transfer, capital availability, human resources and education, shared facilities and a favorable regulatory environment. I would like to address the first two factors.

Medical biotechnology takes novel ideas from the laboratory and develops products for patient use. The funding of biomedical research in the United States has enabled research investigators to make rapid progress in understanding the biochemical causes of many diseases. This in turn leads to new methods of diagnosis and treatment.

I am CEO of Cascade Oncogenics, a company that develops cancer diagnostic tests. Our first product is a test for breast cancer based on cyclin E, a protein that was discovered at Fred Hutchinson Cancer Research Center and Rockefeller University. Cyclin E has a major role in the regulation of cell proliferation. In malignant cells, the concentrations of this protein greatly increase. This provides a way to assess the severity of the cancer and to help in predicting outcome and selecting treatment. Cascade Oncogenics is currently collaborating with local medical institutions to conduct clinical trials for this diagnostic test. The time, so far, to bring this test to the clinic has been only 4½ years since the discovery of cyclin E. The first widely used cancer marker test, prostate specific antigen (PSA) for the early detection of prostate cancer took approximately 14 years from the time that was described until its approval by FDA.

What are the difficulties faced by Cascade Oncogenics and other Oregon biotechnology companies in bringing beneficial products to the patient as quickly as possible? One is to have a critical mass of medical and biological researchers in the state to continue to bring novel technologies to the patient. The investigators we have in Oregon are very good, but there are not enough of them. The universities need additional funding to recruit and retain excellent researchers both basic and clinical We need both.

Oregon research institutions have realized the need for an active technology transfer process and all have responded to that need even in a time of extremely limited resources by changing administrative policies and increasing the professional tech transfer personnel. What are the results? There have been at least 10 companies formed during the last 4 years based on university technology. Of these, eight have been biotechnology companies. The industry is grateful and supports the efforts of the universities to develop technology transfer, but without additional resources they are at risk.

With the increased awareness on the part of universities and their faculty to the advantages of supporting a statewide biotechnology industry, we need additional research faculty to strengthen the research areas where Oregon institutions are already recognized leaders. For example molecular biology at the University of Oregon is ranked in the top 13 percent in the nation. Oregon Health Sciences University has world class research programs in neuroscience and genetic disease defects. These efforts need support. There is also a need to expand clinical research capabilities as we have heard here today. No biomedical products can enter the marketplace without clinical research with patients. By building on our strengths, Oregon can most efficiently develop international recognition. Just as important, from an industry point of view, wide recognition of research expertise attracts larger biopharmaceutical companies and investors.

The second area of major need that I wish to address today is that of capital access. There is a large gap in the availability of capital to fund the growth of biotechnology companies in Oregon. A recent study, partly sponsored by the Oregon Biotechnology Association, has estimated this gap at between $100 and $200 million.

Fortunately in Oregon, we have the Oregon Resource and Technology Development Fund (ORTDF) which is one of the most successful seed investment funds. This was established in 1986 by a far-sighted legislature, but since then its support has been reduced. ORTDF has invested in ten biotechnology companies at the seed stage, most of which are using university technology. However, there is a real need for funding sources to provide follow-on capital as these companies grow. Unlike the computer and electronics companies which have had great success in Oregon in recent years, biotechnology companies require a longer time to bring products to market, especially therapeutic products. Without capital, they will fail.

Several Oregon biotechnology companies are surviving their research and development phases by successfully winning the Small Business Innovation Research (SBIR) Grants and Contracts provided by most federal funding agencies. These excellent awards are absolutely necessary for the survival of biotechnology in Oregon and we would urge their continuing support.

Once again, I thank you for the opportunity to provide these comments. In summary, federal government can best support Biotechnology in Oregon by increasing biological and medical funding for its research institutions and companies and by supporting measures that increase the availability of long term investment capital to fund these companies.

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BIOGRAPHICAL SKETCH OF LYNNOR B. STEVENSON

Lynnor B. Stevenson, Ph.D. is the current Chair of the Oregon Biotechnology Association and Oregon Biotechnology Foundation. She is the founding President/CEO of Cascade Oncogenics, a start-up company developing cancer diagnostics. As Professor and Director of Technology Transfer (part-time) at the University of Oregon, she directs the commercialization of faculty inventions and has assisted in the creation of five new companies. Dr. Stevenson also serves on the Advisory Committee of the Pacific Northwest National Laboratories.

A biochemist, Dr. Stevenson has been involved as corporate officer in the successful start-up of a number of companies including four that are now publicly-held: Creative BioMolecules Inc, Advanced Polymer Systems, Agen Ltd. (Australia) and Univax Corp., (now merged with North American Biologics Inc.). She was the founding President of Heska Corp., a private biotechnology-based animal health company in Colorado. These companies employ 470 in six States.

**STATEMENT OF RICHARD SASS, PI MEDICAL, INC., PORTLAND, OR**

Senator HATFIELD. Mr. Sass.

Mr. SASS. Yes; thank you. I am very pleased to be here. Senator Hatfield, you give new meaning to the word honorable.

I would like to depart from my written testimony. I would like to suggest that I am—I do not have a doctor in front of my name. I am here as a representative of the business community, of someone who has started several companies over a period of my 31-year career. I have fallen in love with the medical and health care related activities, particularly from a business standpoint, since 1981.

As an entrepreneur, I am taking a rather unique approach, I think, to the problem associated with funding. I am here representing three companies today, all of which I have founded, and it might be somewhat interesting for you to hear their names and understand what they are doing.

The first company is PI Medical. It is a medical R&D company. However, it is a for-profit activity. We have been sponsored by several million dollars worth of NIH grants over the last 5 years. I have put in several million dollars because of the shortfall in the grants from the U.S. Government, from the NIH. Roughly we have determined that on a successful grant application we are funded

about 55 percent and we have had to look for additional deep pockets in order to fund the other 45 percent. To date, I have been those deep pockets up until recently.

Another company that has emerged from PI Medical's activity for the express purpose of looking for additional funding mechanisms is a company called National Applied Science. It has actually found some research out of the black hole, I would call it, of research. Also sponsored by the NIH over a 10-year period at the University of Kansas, it is a continuous real-time sensing glucose monitor. It is a little needle sensor.

And a third company that I am here representing today is a newly formed 501–C–3 R&D corporation, probably what I should have done with PI Medical at the outset because we have not been engaged as a for-profit activity at PI Medical; it has been quite the opposite. Some people call it bleeding, other people call it investment. I sit here in front of you today still calling it an investment.

Biosystems Research Institute, the 501–C–3, is my recent attempt at looking at finding additional sources of capital. So when I saw your Clinical Research Enhancement Act, I did a couple of back flips and said, "Well, this is one of those answers. I hope this will happen." I am here to support that activity in any way, shape or form. I would submit to you, however, that the 1 percent that I see on page 2 of the S. 1534 Act suggests that of the $1 trillion spent in the United States health care over the year 1994, only $10 billion, or it sounds like from Dr. Varmus's standpoint closer to $12 billion, was spent on R&D. That equals 1 percent at any rate.

I can imagine that if we added other research efforts from the Department of Defense or other facilities within the U.S. Government that that would perhaps be a larger percent, but I would submit this, that in U.S. business, particularly well-managed Fortune 500 companies, the truly excellent companies that we hear about all the time, their research and development and engineering, it is RD&E, so there is some basic research but probably not more than 1 percent or not more than 2 percent, I'm certain.

But the product development efforts, the engineering efforts in these companies come closer to 10 percent of their revenues, so it seems to me somewhat obvious that we are grossly underfunding a $1 trillion business, that being the health care business in the United States. In fact, I would go further to say that if we do not find ways of accelerating or increasing the amount of dollars, we really are in major decline.

So I think it really is a crisis that we are in the midst of here. I love the comments by Dr. Loriaux, whether clinical research activity is an asset or a liability. Clearly under the budgetary constraints that we all face, it is unfortunate, I think, that some of these expenditures are considered a liability, and, in fact, there are ways of cutting them back and not finding creative ways of funding them.

I would like to take just a minute since the overhead projector is here and I will just move down. No; I think we should have Dr. Kohler come up. He did such a great job. Maybe Dr. Stevenson will be kind enough to put these up, these slides up, one at a time. What these will represent to you are some of my thought processes

as I have gone through, I hope, an orderly evaluation of how I have created various businesses.

In the case of looking for activities that might be commercializable, I have searched in the marketplace for all of the work that various scientists have been working on and in specific, as I mentioned earlier, my area of interest in the medical health care field today is the area of diabetes, so we have looked out there for all of the streams of discoveries, as we call them, and it was my job really as a corporate entity to focus those streams of discovery and to cull through really the thousands of wonderful things that are happening, that I would call them research activities that have been receiving sort of peanut-butter-type of funding, and I have looked for the good sandwiches out there and tried to focus on the ones that I think show the most promise, that would show the most—would show the greatest proof of concept.

One of the interesting things that I find graphically impactful for me is that really from 1987 I have been quite involved in looking for ways of taking what I had been doing in my previous company that I sold in 1991, that was medical ultrasound and video arthroscopic cables and wires and cable assemblies that we became the world leader of, and in 1991 when we sold that company we were at 500 employees here in the State of Oregon.

In 1981, there were two people in the State of Oregon involved in that activity, so quite an outstanding growth perspective. Never made a lot of money during that period from 2 employees up to 500 because of the extraordinary growth that we were having to fund.

But from 1987 I was looking for opportunities to take what we were doing outside of the body and introduce it to dumb things inside the body, dumb things meaning a catheter, for instance, that was just a vehicle to administer some therapeutic drug or food to a patient or whatever, that was simply a transport mechanism for that medium.

What we had learned to do was to make little tiny miniature wires and cables and the people in the data processing world, of course, were improving the memory capacities of chips and what have you, so I envisioned a smart catheter and one where we would see the mounting of chips on little tiny miniature wires all enclosed in the same sized catheter tube that was already being used in the medical industry.

So from 1987 to about 1994, I was exploring that interest and smartening up activities. Well, unbeknownst to me, Prof. George Wilson at the University of Kansas, Dr. Gerard Reach, and John-Claude Klein, a Ph.D., both Reach and Klein were people working in France, George Wilson was at the University of Kansas, in Lawrence, KS, all three of them had been sponsored since 1981 actually by the NIH, and I guess 1985 is the correct time. I am sorry. But they had been running in parallel to me and I did not know these gentlemen.

Along that same period of time and thanks to the good work of the NIH and $164 million application of funds, the diabetes complications and control trials was ongoing from about 1983 to 1993, but totally unbeknownst to myself, quite a large group, 50 scientists, were brought together by me in 1994, all of which were luminaries in the field of diabetes and primarily biosensing and

again, they were traveling along in parallel paths to me but totally unknown to me was their work.

And this is my example really of how various of us can intersect in our lives and, in fact, these biosensor people came together at the Benson Hotel here in December 1994 to examine a technology road map that I had put together, having sorted through quite a number of those discoveries that people had been—literally thousands of people had been working on in their laboratories. And they came together to critique a technology road map and I was looking to sort through those thousands of discoveries and find something that was most promising.

Also during that same period of time and also under NIH sponsorship has been a 25-year career of a man by the name of Buddy Rabner, Dr. Buddy Rabner at the University of Washington, and had been dealing in the areas of engineered bio materials. So all of us have now intersected and have formed together under National Applied Science. We have created a virtual laboratory out of the scientists that came together. We have met now twice. I have had them tied together through the internet. They are also subscribers to our file server. We have a means now of very rapid communication at low cost and the one thing as you can see the dotted line on the bottom we are still looking to have intersect this commercial activity is money. And that is one of the reasons we are here today.

The product that I will show you real quickly here, and I can sense that we are out of time, is a needle sensor. This would fit inside of a 21-gauge introducer needle. It is a couple of inches long with a quadruple laser diced the—just a little bit in from the tip and put a membrane over that. That will sit in subcutaneous tissue, creates glucose molecules and oxygen molecules, pass through the permeable membrane.

They create an electrochemical reaction with the glucose oxidase that is sandwiched within the membrane and hydrogen peroxide is formed. It creates a little—a nanoamp bit of current. It travels the 2 inches down the needle sensor. It excites an ASIC chip. The ASIC chip sends a signal via telemetry to a watch dial and we will be able to provide people with diabetes with a method of continuously reading their blood sugar level via near-field telemetry.

So I think that is maybe all I need to say. One last slide, which is the number slide which several of us worked on, what it really meant when the DCCT said that 60 percent or 70 percent of the complications of diabetes can be reduced if the person with diabetes tightly manages and controls their blood sugar level. I realize that that would not happen in a few years.

So we created a 30-year economic model to determine what it really meant and as we studied it, the numbers—we had to straightline numbers really. We had $103 or $105 billion of the—at that time about $800 billion health care costs in the United States and $105 billion were related to diabetes. So what does it mean if people tightly control and, in fact, the study that the NIH put on called the DCCT was true.

Over a 30-year period, we feel that the hundreds of companies that will be formed that will deliver diabetes management tools—this is without a cure now. This is short of a cure; $52 billion of

that $103 or $105 billion can be saved if in fact the DCCT study is correct. So it is a rather unbelievable return on investment, I think, which is the other way to look at whether or not something is an asset or a liability is what is the return on investment.

PREPARED STATEMENT

The last thing I will say real quickly is tort reform is absolutely critical and underpins this whole thing. There are many of us that are dealing with polymers today that we can get in a research format without any problem, but Du Pont will not provide us product unless we can indemnify them and the small biotech community in the United States does not have the wherewithal to be able to stand up to the indemnification required, so I think very desperately there needs to be some tort reform or the Teflon we put on our needle sensor is absolutely not available, so we might as well just stop right here. Thank you.

Senator HATFIELD. Thank you, Mr. Sass.

[The statement follows:]

PREPARED STATEMENT OF RICHARD G. SASS, CEO, PI MEDICAL, INC., NATIONAL APPLIED SCIENCE, INC., BIOSYSTEMS RESEARCH INSTITUTE, INC., PORTLAND, OR

CLINICAL RESEARCH ENHANCEMENT ACT OF 1996

Comparison between basic research and development and clinical research and development: Basic or fundamental scientific R&D, such as research into cellular and genetic mechanisms of disease, is very important and sometimes opens new realms for understanding human disease. However, most would agree that the vast majority of basic science research never becomes clinically applicable. That is to say, in most cases it does not lead to new techniques for understanding, diagnosing or treating human disease. In fact, the perception of a "black hole" is sometimes the result of basic R&D.

Basic science research cannot be called unimportant, however. Some of the most important discoveries in medical science come from breakthroughs funded by basic research grants or basic research activities conducted by large corporate entities. Even as man's search for the holy grail is a source of constant wonder and amazement, breakthroughs are rarely realized through basic research. An incremental, step-by-step approach is more likely to create success.

In this day and age of customer satisfaction, paying attention to one's knitting, continuous improvement, total quality management and the empowerment of the individual, I believe a collaborative approach to research and development is appropriate; one spawned by an observer closest to the customer—the clinician.

Research and development performed by clinicians is much more likely to be clinically applicable than research by basic scientists. Clinicians who regularly see patients are acutely aware of what is lacking in terms of diagnostic and therapeutic techniques. They are closest to the problem. Because of the lack of funds, however, many clinicians are forced to perform research on their "own nickel" without sufficient time, equipment and/or personnel.

A stabilized funding base is exactly what's needed. I would include within the definition of "stabilized", the notion of long term, multiple-year funding. This would provide for planning and execution of research and development over a sufficient time horizon, to provide not only proof-of-principle in animal models, but actual human studies as well. Additional investigation would provide another degree of risk assessment and create the potential for ultimate market acceptance by adding the human dimension to a complex equation.

If business could be wrapped into the collaborative fabric of clinical research, then an accelerated time-to-market would likely be realizable for the resulting work-products. Longer term funding would also encourage certain clinicians to devote more time to research, thus balancing their practices in a more long term, cost effective manner for the benefit of the healthcare consumer.

In addition to funding issues, another obstacle to clinical R&D is the issue of product liability. Tort reform or, at the very least, some capitation of liability is required. I believe a crisis is brewing in this area. As an example: certain, if not all,

polymers are unavailable for implantable applications inside the human body to small, medium and most large size companies today as a result of an unfavorable tort environment regarding product liability. Only the very largest of companies can procure polymers from Du Pont and then only with indemnification.

These large companies typically do not move with entrepreneurial speed and are often so risk averse as to stymie innovation and creativity. Innovation and creativity are typically spawned by collaborations of small companies or small self-directed work teams that are entrepreneurial and responsive by nature.

If capital creation components of healthcare reform, including adequate funding for clinical research, is not forthcoming, then many excellent clinical research projects will not become commercial realities. This, in large part, will be due to the analysis-paralysis, risk aversion and general bureaucratic redtape generated by an ever less responsive, capital-constrained, overly-regulated environment. This all leads to unaccountability and a reduction of personal responsibility. All this is contrary to an ever increasing environment of managed care that stresses a need for more and more personal responsibility if our human condition is to be improved.

Examples of innovative clinical discoveries which have changed how medicine is practiced:

*Cardiac pacemaker.*—In the early 1950's, a practicing thoracic surgeon in Toronto, Wilford Bigelow, found that the heart could be directly paced with electrical impulses. After observing Dr. Bigelow's technique, Dr. Paul Zoll, a practicing cardiologist at Beth Israel Hospital in Boston, developed the first external pacemaker. (When he was training as a resident in Boston, Dr. Wayne Rogers, now a cardiologist at Good Samaritan Hospital in Portland, worked closely with Dr. Zoll. Dr. Rogers provided this historical capsule.) A number of improvements in pacemaker design have been made by many other clinicians working in collaboration with industry since that time.

*Artificial heart valve.*—Dr. Albert Starr, now of St. Vincent's Hospital in Portland, developed and implanted one of the first artificial heart valves.

*Hemodialysis system.*—Dr. Richard Drake, working with a bioengineer, pioneered one of the first hemodialysis coils (the Drake-Willock coil) to cleanse nitrogenous wastes from the blood of persons with kidney failure. Prior to dialysis, all persons with kidney failure died. Dr. Drake, who practiced for many years as a kidney specialist at Good Samaritan Hospital, recently retired and now serves on the board of National Applied Science.

*Continuous insulin pump.*—Dr. John Pickup, a practicing diabetologist at Guy's Hospital in London, developed the first continuous external subcutaneous insulin pump in the late 1970's. A group of clinicians at Yale, including Drs. Tamborlane and Sherwin, developed an insulin pump in the United States at about the same time.

Recently, the Diabetes Control and Complications Trial (DCCT) demonstrated that individuals whose diabetes was tightly controlled were much less likely to develop diabetic complications than those whose diabetes control was less strict.

An example of an innovative clinical research work-in-progress that will provide people with diabetes another mechanism to tightly manage and control blood glucose levels and thereby dramatically reduce the complications of the disease, leading to an improvement in quality of life.

*Continuous, Real-Time Sense, Glucose Monitor.*—The Wilson/Reach/Klein amperometric needle (bio)sensor was funded under various NIH sponsored research grants in a multi-year collaboration between a team of clinical researchers and University-based scientific researchers. This product is now in the early stages of commercialization by National Applied Science, Inc.

IN SUMMARY

Clinical Research is more relevant—closest to customer.
Clinical Research encouraged—stabilized, adequate, multi-year funding.
Collaboration with industry—improved time-to-market.
Tort Reform is a necessity—product liability capitation.
Accelerate regulatory approval—self certification as in European Union.

## LACK OF YOUNG, TRAINED CLINICAL RESEARCHERS

Senator HATFIELD. Dr. Stevenson, with your background both in academia and private industry, can you elaborate on the relative lack of young, trained clinical researchers and where do you see that pool of young investigators going and why?

Dr. STEVENSON. Yes; I think that as has been pointed out today, the M.D.'s are tending more into becoming clinicians and the Ph.D.'s are being split between basic research in research institutions where it is becoming increasingly difficult to get NIH funding to do research and into biotechnology companies.

But from what I have observed, I mean, this will continue to happen, but unless the biotechnology company, the biotechnology industry, can build rapidly enough, which I think it has the potential to do and it certainly has—there's scope, a range, of products out there to be developed. I think they could absorb a lot of the—well, both basic and clinical research to some extent.

But I do not think that decreases the need at all for having clinical investigators within academic institutions to do just the kind of work that Dr. Loriaux talked about, because some of that work has to be done in order to understand what we are doing with this rapid development of products.

Senator HATFIELD. There have been observers who have said that the increasing number of patients going into managed care will reduce the numbers of possible persons who are subject to clinical trials. Have you observed that or what is your thought about that observation? And the question also follows, what is the private sector doing today or what are they experiencing in enrolling patients in clinical trials?

Dr. STEVENSON. Well, one of the things we are talking about, certainly, is trying to talk with the managed care organizations but we realize that the return on the investment for them probably isn't fast enough. We have to show them—in order to persuade them to test products in their situation, we would have to show them a relatively rapid decrease in costs.

Now while we think that we can show a decrease in cost over time, Richard's example was pretty long term for a monitoring product or a—but I think there is this timing balance that we keep running into with every aspect. Whether it is developing a new biotechnology in a State that does not have one or developing—trying to increase clinical research, there is a gap that requires investment and somehow I think we have to convince the managed care organizations that it is worth their while to make that investment for the sake of the reduction in costs that they will get longer term.

Senator HATFIELD. Mr. Sass, do you see the private sector playing an increasing collaborative role in clinical research? And what about the proposition that some have said, that Government should attend only to basic science research and let the private sector fund the translational research?

Mr. SASS. Well, I think it—I think the No. 1 question that you had relative to a collaboration with the private industry is absolutely critical. I think that no one segment of the world can do it alone. I think it definitely in—we talk about partnerships and partnering and I think some of us can spell that and not everybody walks the talk, so there is, I think, even some fundamental problems in the—in our society with regard to relationships even. But the partnering with industry is absolutely essential, I believe.

The second half of your question was about——

Senator HATFIELD. Leaving basic science research to Government and translating it to the private sector.

Mr. SASS. And again, I think what you are touching on here really is this definitional issue of basic research and I think there are at least the three or four steps along the way in the commercialization process and the clinical research effort is so tightly connected to basic research that I think it belongs still at that governmental level with our tax dollars.

It is not that the Government is another entity; it is an extension of you and I, and I think the way businesses are organized is to commercialize products that have shown proof of concept and basic research does not necessarily show proof of concept, at least what I have seen. It is, in fact, the clinical research area that perfects the proof of concept.

And it is one thing to do research in animals and that is a very valuable component, but unless research can be extended into human subjects and in some statistically valid number of human subjects, we really don't know whether or not something is the right pathway.

Senator HATFIELD. I saw a study with the Pacific Northwest Universities, research universities involved. The studies showed the amount of revenue developed out of the basic science at those universities and where the estimates of the total dollars in a period of time of either device, product, drug or whatever it was, was primarily the benefit to the investor and the private enterprise and the university shared in a very small part of that large revenue.

Do you see that as a possible fact that you could attest to and/or how do you think the universities might benefit a little more from the product or the results of basic science in terms of helping to replace some of the diminishing—I say diminishing, beginning in 1998, the diminishing dollars that will be going into basic research at the NIH and other programs?

Mr. SASS. Again, in a partnership, it has to be a win-win thing in any relationship for it to work well, so I think the technology transfer component that I know exists and we actually are participating in an STTR program, the Copely Implant Program, that is funded by an STTR phase 2 at this time.

There is a component in there, at least I am not sure whether it is mandated to us, but we are planning as the technology gets developed to have ongoing future revenue shared in the form of royalties. They will be—at least as we are seeing this composed that there will be ongoing sponsorship of additional research from the corporation back again to the department from which these scientists emerged.

But I think the simple answer is a royalty screenback and I think OHSU has some wonderful examples, I think, of royalties coming back and moneys being provided that are over and above royalties even from appreciative business, if you will.

Dr. STEVENSON. Could I address that too? This is a topic that I have thought a lot of about and I think there are a number of ways that the universities can benefit from a strong industry. I think the biotechnology industry has really provided the leads for this simply because that tie is so close to the research.

First of all, as Richard said, there is a royalty strength. In some cases, I think the universities can benefit from holding equity in the companies so that even if the particular technology from the

university does not succeed, they will still benefit from having licensed their technology to a local company, particularly if it is local.

Second, I think this is a chance at sponsored research coming back to the university, not only the companies that I have been involved with, we have not only funded specific applied research, but we have helped to fund and have given gifts to universities to continue the surrounding basic research to take it forward. And then I think these—the transfer clinical trials sponsorship which has been referred to today, the kind of thing that pharmaceutical companies sponsored but also biopharmaceutical and biotechnology companies sponsor.

And then last I think the economic growth in the region where companies grow and become profitable will lead to further collaborations and further spinouts that benefit everyone in the State and feed back that way. There's the hiring of graduates so that they stay in the State and do not leave, and so I really think there is a number of reasons for universities, businesses, and States to promote these kinds of interactions. I think there are tremendous benefits to speak of.

Senator HATFIELD. Well, thank you very much. Let me just make a few comments in closing the hearing. I think that when we look over the last year's experience, 18 months, it becomes very obvious that the overall direction of the Federal Government's spending is downward and when you look at the President's budget proposal for NIH for 1996, it called for a major reduction in the $11.3 billion that we fund annually.

It has been on the increase since about 1981, but the House of Representatives has further decreased the funding for NIH for 1996. The Senate was not to be outdone. In the budget resolution process where it sets the caps for various and sundry programs, the budget committee in the Senate outdid the House in its reductions and it was really what I called a prelude to disaster. It was not a matter of reducing the spending levels of NIH; it was a matter of decimating and then by the year 2002 you would have found a destruction, I think, of this magnificent enterprise of science research conducted through the NIH.

Because of the response of people from all over this country, particularly in the 12,000 centers of medical education and research, we were able to mobilize an action on the floor of the Senate and defeated the proposal handily by an 84-to-15 vote, the only change made in the budget resolution. I say that because as a result of that, for 1996–97, we increased in our bill, which has yet to be signed by the President, the NIH budget by 5.7 percent over 1995. Now that gave everyone a great—people who were concerned about medical research, a great thrill, a great optimism.

I want to reiterate at the time that we introduced our bill on the floor of the Senate for the medical research factor in NIH, that under the general overall policies that are being mobilized and are on track, we cannot sustain that in the outyears and I do not think we should get so shortsighted with 1996–97 that we ignore what is going to happen in 1997–99, and that is a diminution. It is going to be a strong diminution of those levels of funding, not even to consider the so-called inflation factor.

And that is why we have to do two things. It seems to me we have to shore up those vulnerable areas within our present program. This is the purpose of this bill: to address the cause and the needs of clinical research. But also, as has been referenced today, we must find an independent sourcing of revenue for the NIH and medical research that does not rely so completely upon the annual appropriation process of the Congress and the President.

That is why a couple of years ago Senator Harkin of Iowa and I proposed this medical research trust fund. We can add $4 to $6 billion a year for medical research funds from a 25-cent tax on cigarettes and as a reformed smoker, I support that very strongly, besides the medical reasons. But we must pursue those twin directions at this time or twin goals.

I am happy to say that even though this is an Appropriations Committee hearing and it is considering an authorizing bill, which we do not have the authority in the Appropriations Committee to enact, I have the votes on the Appropriations Committee, but this now becomes a jurisdictional question of the authorizing committee.

I am very happy to say that I have discussed this matter with Senator Kassebaum, who is the chairperson of that committee, of the authorizing committee, and she has been working for quite some time on what she calls a NIH, National Institutes of Health, revitalization bill. It is reviewing the entire mission of NIH and seeing how we can help strengthen the basic mission structure, and she is very sympathetic to this proposal and I have every expectation of having that incorporated, this proposal incorporated, in her authorization bill if we can get the authorization bill through. But at least we won't know unless we try. We are going to give it a hell of a try.

So I merely want to take this moment again to issue a call to keep mobilized as we have mobilized in the effort to save the NIH from destruction in the budget resolution and keep that kind of dry powder to move on to these other matters that mean so much in the long term for our Nation and the health of its people.

## CONCLUSION OF HEARING

I want to thank again our host, the Oregon Health Sciences University, and President Kohler. I want to thank again Dr. Varmus for making the trip and for those of you, Dr. Williams and Dr. Farley, who traveled some distance as well to participate and to close the hearing and wait until you hear the next call to arms.

The subcommittee will stand in recess subject to the call of the Chair.

[Whereupon at 4:35 p.m., Thursday, April 11, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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